

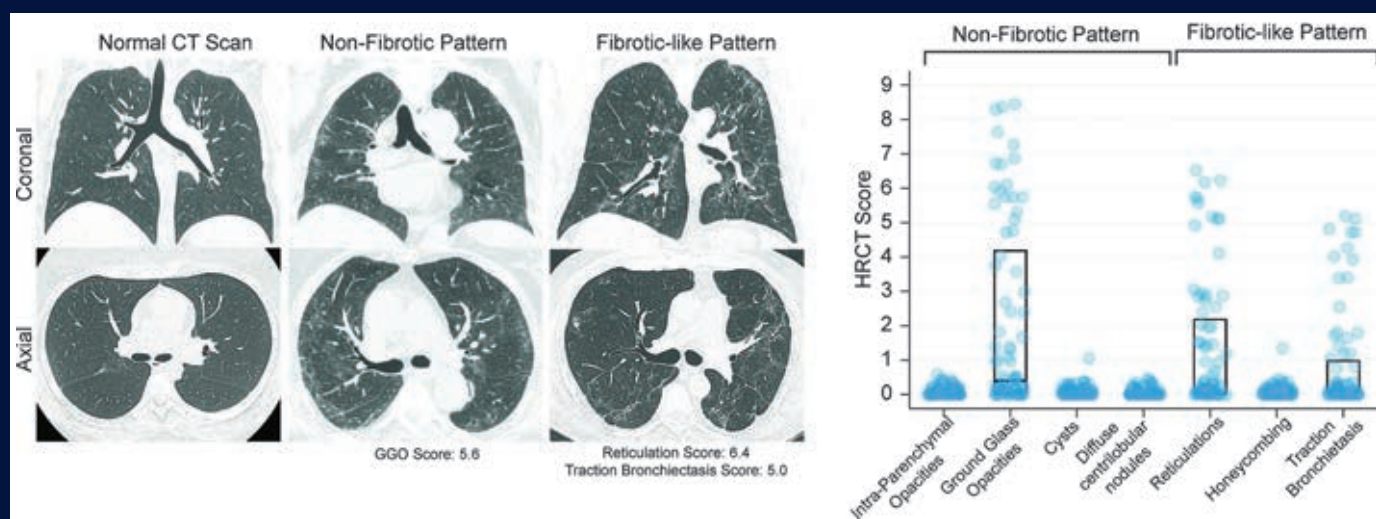
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LABA-LCS

INHALAÇÃO

TOMADA



Revinty
furoato de fluticasona + vilanterol ELLIPTA
ELE CONTROLA

O perfil de segurança de Revinty foi validado em ensaios clínicos de grande escala, como o SUMMIT⁴ (n=4121) e SLS na Asma (n=2114)¹

1) Woodcock A *et al.* Lancet 2017; 390:2247–2255. 2) Bateman ED *et al.* Thorax 2014; 69:312–319. 3) GINA. Global strategy for asthma management and prevention, 2021. Available at: <https://ginasthma.org/linha-reportis/> (Acedido: dezembro 2021). 4) Vestbo J *et al.* Lancet 2016;387:1817-1826. ICS: Corticosteroide inalado; LABA: Agonista β_2 de longa duração de ação.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM. NOME DO MEDICAMENTO Revinty Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Revinty Ellipta 92/22 mcg: Cada inalação disponibiliza uma dose administrada de 92 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 100 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifrenatato). Revinty Ellipta 184/22 mcg: Cada inalação disponibiliza uma dose administrada de 184 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 200 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifrenatato). Cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose **INDICAÇÕES TERAPÉUTICAS** Asma: Revinty Ellipta 92/22 mcg e 184/22 mcg está indicado para o tratamento regular da asma em adultos e adolescentes com idade ≥ 12 anos em que a utilização de um medicamento contendo uma associação (agonista beta₂ de ação prolongada e corticosteroides para inalação) é adequada: doentes que não estão adequadamente controlados com corticosteroides para inalação e com agonistas beta₂ de curta duração de ação 'conforme o necessário'; doentes que estão já adequadamente controlados com corticosteroides para inalação e com agonistas beta₂ de ação prolongada. **DPOC:** Revinty Ellipta 92/22 mcg está indicado para o tratamento sintomático de adultos com DPOC com um FEV₁ previsível normal <70% (após o broncodilatador) com antecedentes de exacerbação apesar da terapêutica regular com um broncodilatador. **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Asma (92/22 mcg e 184/22 mcg) Adultos e adolescentes ≥ 12 anos Deve considerar-se uma dose inicial de uma inalação de 92/22 mcg uma vez por dia para adultos e adolescentes ≥ 12 anos que requeiram uma dose baixa a média de corticosteroides para inalação em associação com um agonista beta₂ de ação prolongada. Se os doentes não estiverem corretamente controlados com 92/22 mcg, a dose pode ser aumentada para 184/22 mcg. Os doentes devem ser regularmente reavaliados. A dose deve ser titulada para a dose mais baixa com a qual é mantido um controlo efetivo dos sintomas. Revinty Ellipta 184/22 mcg deve ser considerado para adultos e adolescentes ≥ 12 anos que requeiram uma dose mais elevada de corticosteroides para inalação em associação com um agonista beta₂ de ação prolongada. Os doentes normalmente verificam uma melhoria na função pulmonar 15 minutos após a inalação. É necessário o uso diário regular para manter o controlo dos sintomas de asma e o uso deve ser continuado mesmo quando esta é assintomática. Se os sintomas surgirem no período entre as doses, deve ser utilizado um agonista beta₂ de curta duração de ação, por inalação, para o alívio imediato. A dose máxima recomendada é 184/22 mcg 1x/dia. Crianças <12 anos A segurança e a eficácia ainda não foram estabelecidas na indicação para a asma. **DPOC (92/22 mcg) Adultos ≥ 18 anos** Uma inalação 1x/dia. Os doentes normalmente verificam uma melhoria na função pulmonar 16-17 minutos após a inalação. **População pediátrica** Não existe utilização relevante na população pediátrica para a indicação de DPOC. **Populações especiais** Idosos (> 65 anos) e Compromisso renal Não é necessário ajustar a posologia. **Compromisso hepático** Estudos revelaram um aumento na exposição sistémica ao FF. Devem tomar-se precauções na definição da posologia em doentes com compromisso hepático que possam estar em risco mais elevado de reações adversas sistémicas associadas a corticosteroides. Para os doentes com compromisso hepático moderado ou grave a dose máxima é de 92/22 mcg. **Modo de administração** Via inalatória. Deve ser administrado à mesma hora do dia, todos os dias. Se uma dose for omitida, deve tomar-se a próxima dose à hora habitual no dia seguinte. Após inalação, os doentes devem enxaguar a boca com água sem a engolir. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram cefaleia e nasofaringite. Com a exceção de pneumonia e fraturas, o perfil de segurança foi semelhante em doentes com asma e DPOC. Durante os estudos clínicos, pneumonia e fraturas foram mais frequentemente observadas em doentes com DPOC. **Infeções e infestações** Frequentes Pneumonia, infeção do trato respiratório superior, bronquite, gripe, candidíase da boca e da garganta **Doenças do sistema imunitário** Raras Reações de hipersensibilidade incluindo anafilaxia, angioedema, erupção cutânea e urticária **Doenças do metabolismo e da nutrição** Pouco Frequentes Hiperglicémia **Perturbações do foro psiquiátrico** Raras Ansiedade **Doenças do sistema nervoso** Muito frequentes Cefaleia Raras Tremor **Afeções oculares** Pouco frequentes Visão turva **Doenças cardíacas** Pouco frequentes Extra-sístoles Raras Palpitações, taquicardia **Doenças respiratórias, torácicas e do mediastino** Muito frequentes Nasofaringite Frequentes Dor orofaríngea, sinusite, faringite, rinite, tosse, disfonia Raras Broncospasmo paradoxal **Doenças gastrointestinais** Frequentes Dor abdominal **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia, dorsalgia, fraturas, espasmos musculares **Perturbações gerais e alterações no local de administração** Frequentes Pirexia. **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** outubro 2021. **APRESENTAÇÃO:** Revinty Ellipta 92 mcg+22 mcg, 30 doses; Revinty Ellipta 184 mcg+22 mcg, 30 doses. **Regime de comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. **Medicamento Sujeito a Receita Médica.** 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. 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 & C^ª, S.A., -À 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_PT211117

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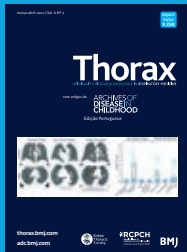
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Editorial

Nos últimos meses confirmou-se o que já se esperava. Novas variantes do SARS-CoV-2, de alta contagiosidade, mas com menor impacto em termos de morbilidade e de mortalidade, traduzindo também o efeito benéfico da vacinação. A pandemia entrou claramente numa nova fase embora continue bem viva na nossa agenda clínica.

E, simultaneamente, regressaram com grande expressão muitos outros agentes infecciosos. Que surgiram de um modo previsível, mas também “fora de época”, como se verificou, por exemplo, com o vírus sincicial respiratório.

Mas agora chegou a Primavera. Os alérgenos circulam cada vez mais no ar que nos rodeia. E este ano até vieram acompanhados por poeiras do deserto. Por isso, atenção. Para os alérgicos estes podem ser os piores meses do ano, com sintomas graves e muito perturbadores da qualidade de vida. E alergias prolongam-se por todo o ano. Afetam uma percentagem enorme da população e não escolhem idade ou género.

Vamos então continuar a discutir em conjunto as melhores estratégias para diagnosticar precocemente, abordar e tratar com eficiência, pois o controlo está ao alcance dos nossos doentes.

Neste número, Arnold et al. refletem sobre a aerossolização do SARSCoV-2, sugerindo que no futuro diferentes estratégias de minimização do risco infeccioso podem vir a ser implementadas, estando por esclarecer a sua eficácia na proteção, nomeadamente dos profissionais de saúde.

Epidemiologia da tuberculose em idade pediátrica e as desigualdades de saúde em crianças e jovens durante a Pandemia de COVID-19, avanços na avaliação da gravidade da apneia obstrutiva do sono com recurso a *smartphones*, a expressão de fenótipos versus genótipos da DPCO e ações para promover a atividade física destes doentes, são apenas alguns dos temas que Vos propomos para reflexão.

E não queríamos terminar sem agradecer por nos continuarem a acompanhar com as Vossas leituras.

Vivemos uma época muito conturbada, com múltiplas dimensões que nos afetam, que vão da Saúde Pública à dignidade da pessoa humana. Temos múltiplas necessidades. E temos de tentar fazer cada vez melhor.

Por todos nós. Os que estão aqui e os que aqui tão perto esperam poder contar connosco...

Até já.

Mário Morais de Almeida

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A tosse e os espirros disseminam doenças: e os procedimentos 'geradores de aerossóis'?

David T Arnold,¹ Fergus W Hamilton,^{2,3} Ed Moran⁴

A pandemia da COVID-19 resultou na utilização generalizada de pressão positiva contínua nas vias respiratórias (CPAP) e de sistemas de oxigénio nasal de alto fluxo (HFNO) para apoio respiratório, tendo o primeiro demonstrado recentemente reduzir a necessidade de intubação e ventilação mecânica, aliviando a pressão nos cuidados intensivos e melhorando os resultados.¹

Uma das principais preocupações continua a ser o risco teórico de aerossolização do SARS-CoV-2, sendo a CPAP e o HFNO atualmente considerados como "procedimentos geradores de aerossóis" (PGA). Esta classificação, aprovada pela Saúde Pública de Inglaterra, a OMS e o CDC dos EUA, dicotomiza os procedimentos médicos em procedimentos que potencialmente geram aerossóis infecciosos (partículas mais pequenas, geralmente <5µm com o potencial de permanecerem suspensas durante períodos prolongados) e os procedimentos que não o fazem.² Assim, aconselha-se o aumento das precauções de controlo de infeção (por exemplo, máscara de proteção de partículas suspensas, aumento da ventilação, criação de "bolhas") quando os doentes realizam PGA mas estas não são obrigatórias fora destes ambientes.

A evidência que suporta este conceito de PGA é largamente baseada na observação epidemiológica, particularmente da pandemia de SARS, com dados físicos limitados que apoiam o papel da geração de aerossóis na maioria dos PGA.³ Estudos realizados durante a pandemia estão a minar o paradigma dos PGA, com evidências convincentes de que o aerossol gerado em atividades respiratórias normais excede a quantidade limitada gerada por (quase) todos os PGA testados.^{4,5} Até à data, poucos estudos tentaram medir o vírus infeccioso real durante os PGA suspeitos, dadas as dificuldades de realizar estas medições.

Neste número, Winslow *et al* fornecem dados úteis sobre a aerossolização do SARS-CoV-2 por amostragem aérea enquanto os doentes são submetidos tanto a HFNO como a CPAP.⁶ Trinta doentes admitidos com COVID-19 foram incluídos neste estudo observacional. Ao co-inscrever os participantes que estavam a participar no RECOVERY-RS,¹ um ensaio que aleatorizou indivíduos para diferentes modalidades de apoio respiratório, foram reduzidos os confundidores entre os grupos. Foram comparados três grupos de 10 participantes, que receberam oxigénio suplementar através de máscara Venturi, CPAP com filtro viral padrão ou HFNO com uma taxa de fluxo típica de 50-60L/min. Usando um protocolo de amostragem idêntico para

todos os participantes, foram realizados ensaios RT-PCR para ARN humano e de SARS-CoV-2 a partir do ar e ambiente clínico imediato. Verificou-se que, enquanto 21/30 (70%) participantes testaram positivo para ARN de SARS-CoV-2 na nasofaringe, apenas 30% apresentaram um resultado positivo do ar amostrado com cargas virais mais baixas associadas (valores Ct mais elevados). A partir das superfícies circundantes, foi identificado mais ARN viral, sendo que 46% apresentaram pelo menos uma amostra positiva e o chão foi a superfície mais comumente afetada. Essencialmente, não foi detetada qualquer diferença no ARN viral entre os participantes em termos do tipo de suporte respiratório a ser utilizado. É de notar que, embora a cultura viral tenha sido tentada em todas as amostras positivas de PCR, nenhuma amostra de ar e apenas uma amostra nasofaríngea se revelou positiva. Os doentes foram amostrados em média 12 dias após o início dos sintomas, o que talvez não seja surpreendente, dados os elevados valores de Ct e a dinâmica de infeção por SARS-CoV-2 em doentes imunocompetentes.⁷

O presente estudo reforça a evidência crescente de que a classificação dos PGA não é útil na definição dos riscos de transmissão. Resultou em medidas excessivamente cautelosas para certos ambientes, exigindo PPE completos para todas as intubações⁴ e impedindo os familiares de visitar os doentes mais enfermos, ao mesmo tempo que subestima o risco noutros, tais como o pessoal do departamento de emergência recolher esfregaços de doentes recentemente sintomáticos, o pessoal da enfermaria prestar cuidados pessoais a doentes com COVID-19 conhecida e o pessoal não clínico limpar pisos contaminados.

Estes resultados também estão correlacionados com estudos mecanísticos de geração de aerossóis a partir de procedimentos de suporte respiratório que demonstraram que a respiração, a fala e a tosse geram mais aerossóis do que a CPAP ou o HFNO.^{5,8} Este facto, e a diminuição da infecciosidade dos doentes com COVID-19 no decurso de uma hospitalização, explica parcialmente as baixas taxas de seropositividade de SARS-CoV-2 entre o pessoal dos cuidados intensivos em comparação com outros grupos de pessoal com maior contacto com o doente,^{9,10} apesar das evidências iniciais sugerirem cargas virais mais elevadas nestes doentes.

Em suma, é claro que a transmissão por aerossol de SARS-CoV-2 ocorre e há evidências crescentes de que o risco de infeção em ambientes hospitalares tem uma relação negativa com a orientação histórica dos PGS. Dentro dos contextos de cuidados de saúde, sempre foi aceite um determinado nível de risco. Ao longo de toda a pandemia, as políticas nacionais procuraram, de forma pragmática, minimizar, em vez de eliminar, todo o risco, adaptando-se ao longo da pandemia de acordo com a classificação inicial de SARS-CoV-2 enquanto doença

infecciosa de elevadas consequências. Contudo, neste momento, as evidências sugerem que o equilíbrio do risco está colocado exatamente no lugar errado, com um aumento de PPE obrigatório nas situações em que o aerossol é menos provável e as pessoas estão menos infecciosas - por exemplo, as que trabalham na UCI ou que cuidam das pessoas a receber CPAP - e não naquelas em que o aerossol é mais provável e as pessoas mais infecciosas - tais como os doentes com tosse e infeção precoce nas unidades de admissão e enfermarias gerais.

Insistir nas precauções por via aérea para todo o pessoal de saúde em contacto com possíveis doentes com SARS-CoV-2 será extremamente dispendioso - e, como qualquer utilizador de PPE sabe, desconfortável - para ganhos cada vez mais limitados no caso de a transmissão de SARS-CoV-2 cair e de os potenciais riscos de infeção serem atenuados pela vacinação. Por outro lado, é pouco provável que a remoção de todas as precauções por via aérea seja considerada aceitável por aqueles que trabalham em áreas habituadas a tais precauções e pareceria imprudente dada a evidência emergente de uma diminuição da imunidade e a perspetiva de variantes cada vez mais transmissíveis. Provavelmente, apenas uma coisa é clara: no futuro, aguardam-se decisões pouco uniformes para aqueles que têm a tarefa de decidir a política de controlo de infeções.

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REFERENCES

- Perkins GD, Ji C, Connolly BA. An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19. *Medrxiv* 2021.
- Klompas M, Baker MA, Rhee C. Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. *JAMA* 2020.
- Tran K, Cimon K, Severn M, et al. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012;7:e35797.
- Brown J, Gregson FKA, Shrimpton A, et al. A quantitative evaluation of aerosol generation during tracheal intubation and extubation. *Anaesthesia* 2021;76:174-81.
- Hamilton F, Gregson F, Arnold D. Aerosol emission from the respiratory tract: an analysis of relative risks from oxygen delivery systems. *Medrxiv* 2021.
- Winslow RL, Zhou J, Windle EF, et al. SARS-CoV-2 environmental contamination from hospitalised patients with COVID-19 receiving aerosol-generating procedures. *Thorax* 2022;77:259-67.
- Cevik M, Kuppalli K, Kindrachuk J, et al. Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ* 2020;371:m3862.
- Gaeckle NT, Lee J, Park Y, et al. Aerosol generation from the respiratory tract with various modes of oxygen delivery. *Am J Respir Crit Care Med* 2020;202:1115-24.
- Jones CR, Hamilton FW, Thompson A, et al. SARS-CoV-2 IgG seroprevalence in healthcare workers and other staff at North Bristol NHS trust: a sociodemographic analysis. *J Infect* 2021;82:e24-7.
- Shields A, Faustini SE, Perez-Toledo M, et al. SARS-CoV-2 seroprevalence and asymptomatic viral carriage in healthcare workers: a cross-sectional study. *Thorax* 2020;75:1089-94.

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Epidemiologia, características clínicas e resultados de tuberculose incidente em crianças no Canadá em 2013-2016: resultados de um estudo de vigilância nacional

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RESUMO

Objetivo A doença da tuberculose infantil é difícil de diagnosticar e de gerir e é uma causa subreconhecida de morbilidade e mortalidade. Os dados reportados do Canadá não se concentram na tuberculose infantil nem captam os principais detalhes epidemiológicos, clínicos e microbiológicos. O objetivo deste estudo foi avaliar a demografia, a apresentação e as características clínicas da tuberculose infantil no Canadá.

Métodos Conduzimos uma vigilância prospetiva entre 2013 e 2016 de mais de 2700 pediatras e programas de tuberculose verticais para a tuberculose incidente em crianças menores de 15 anos no Canadá através do Programa Canadiano de Vigilância Pediátrica (CPSP).

Resultados No total, estão incluídos 200 casos neste estudo. A tuberculose foi intratorácica em 183 pacientes, dos quais 86% apresentaram um envolvimento exclusivamente intratorácico. Em 16 casos (8%), ocorreu tuberculose do sistema nervoso central. Cinquenta e um por cento dos casos foram hospitalizados e 11 (5,5%) foram internados em unidade de cuidados intensivos. Foram reportadas reações adversas aos medicamentos em 9% dos casos. O caso original, mais frequentemente um parente em primeiro grau, foi identificado em 73% dos casos. Cinquenta e oito por cento dos casos relatados foram de crianças indígenas nascidas no Canadá. As taxas de estudo estimadas de casos reportados (por 100 000 crianças por ano) foram de 1,2 no total, 8,6 para todas as crianças indígenas e 54,3 para as crianças inuítes.

Conclusão A tuberculose infantil pode causar uma morbilidade e uma utilização de recursos significativas. As principais geografias e grupos apresentam taxas de incidência muito elevadas. A eliminação da tuberculose infantil no Canadá irá exigir esforços comunitários bem financiados que se concentram nestes grupos de maior risco.

BACKGROUND

Globally, there were an estimated 10 million new cases and 1.4 million tuberculosis (TB)-related deaths in 2018.¹ In Canada, there are on average 1800 incident cases of TB disease per year with approximately 3% of disease occurring in children younger than 15 years.² In Canada, Indigenous peoples and foreign-born individuals are disproportionately affected by TB.³ Compared with adult TB, childhood TB disease is more difficult to diagnose, presents unique management challenges⁴⁻⁵ and is an under-recognised cause of morbidity.^{6,7}

TB is a reportable disease at the federal and provincial/territorial levels in Canada. However, available data do not capture important details including the type of disease, use and results of diagnostic tests, rates of culture confirmation and hospitalisation, follow-up data, rates of adverse drug reactions (ADRs), rates in specific childhood populations and

What is already known on this topic?

- Childhood tuberculosis is under-reported and under-researched but, globally, is a major hidden cause of childhood mortality.
- According to the Public Health Agency of Canada, childhood tuberculosis accounts for about 3% of all cases in the country.
- National data lacked important clinical, treatment and epidemiological detail including methods of diagnosis that is needed to improve diagnosis, management and control.

What this study adds?

- This study prospectively surveyed clinicians and programs managing childhood tuberculosis and provides more epidemiologic and clinical detail than published Canadian data.
- There is substantial variation in regional incidence and remarkably high rates of tuberculosis in Indigenous Canadians who accounted for more than half of cases.
- This study demonstrated high rates of hospitalisation, central nervous system infection with intensive care unit admission and a substantial rate of adverse drug reactions.

whether source cases were identified. To address these gaps, we conducted a multi-year prospective surveillance study of incident TB disease in children under the age of 15 in Canada using the Canadian Paediatric Surveillance Program (CPSP). Additional pertinent background information is given in the online supplemental appendix.

METHODS

The CPSP, a joint project of the Public Health Agency of Canada (PHAC) and the Canadian Paediatric Society, conducts active monthly national surveillance of over 2700 participant paediatricians and paediatric subspecialists for certain childhood disorders. For this study, we also included non-paediatricians from the TB programmes of Alberta, Saskatchewan, Nunavut, the Northwest Territories and British Columbia. We aimed to identify incident cases of childhood TB between October 2013 and September 2016 and follow-up every 6 months until 6 months post-treatment completion.



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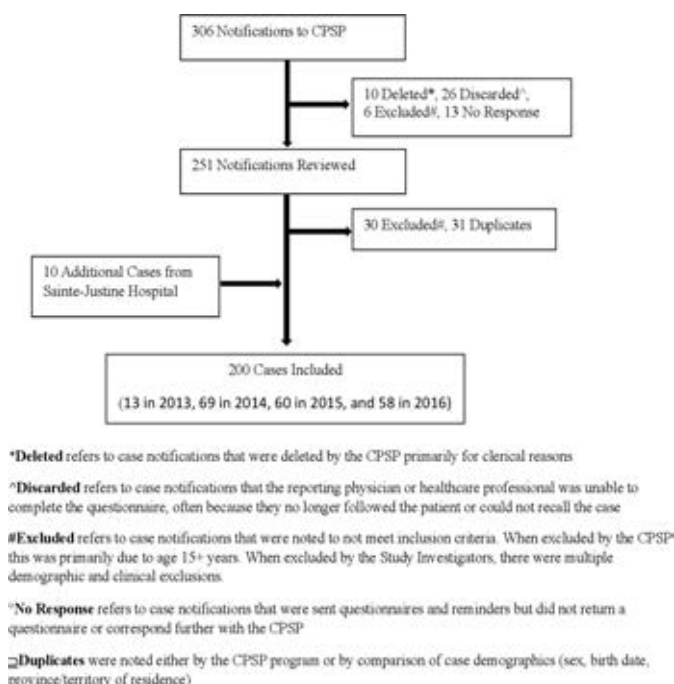


Figure 1 Flowchart of cases notified, excluded and included. CPSP, Canadian Paediatric Surveillance Program.

Pertinent data from the TB programme at Hôpital Sainte-Justine in Montréal, Québec, were retrospectively obtained in May 2017 outside of the CPSP platform. The protocol (<https://www.cpsp-cpsca/uploads/studies/childhood-TB-protocol.pdf>) initially used existing international case definitions for the diagnosis of intrathoracic childhood TB,⁸ however, revised criteria for intrathoracic TB were published in 2015 so we reviewed and reclassified all cases as confirmed or unconfirmed by consensus adjudication by three authors (SKM, RJPG, IK) according to the new criteria.⁹

We calculated population-based age-specific rates of reported cases using 2016 population data¹⁰; for those <1 year of age we used number of live births. Due to potential under-reporting, rates presented here represent the lowest possible estimate of

incidence of childhood TB for specific groups. Rates for Indigenous populations were calculated using denominators from Statistics Canada Aboriginal Population Profile.¹¹ Details of study's ethics approvals are provided in the online supplemental appendix.

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FINDINGS

From October 2013 to September 2016, an average of 2536 monthly reporting forms were sent by CPSP and response rates averaged 81%. The number reported and reasons for exclusions are shown in figure 1 and 200 cases met the study case definition. Eighty cases (40%) were microbiologically confirmed and 116 (58%) were categorised as unconfirmed. The remaining 4 cases were categorised as presumed or difficult to classify. Sixty-six (36%) and 20 (53%) of intrathoracic and extrathoracic cases, respectively, were microbiologically confirmed.

The calculated minimum overall rate of reported cases of childhood TB during the study period was 1.2 per 100 000 per year compared with an approximate notification rate to PHAC of 1.6/100 000.¹¹ Comparisons with data reported by the PHAC are shown in the online supplemental appendix. Key demographics of cases reported to CPSP are shown in table 1. Reports by age group were 2.4 per 100 000 live births in children under 1 and 1.8, 0.6 and 0.9 per 100 000 population for the age groups 1–4, 5–9 and 10–14 years, respectively. Most cases (n=116, 58%) occurred in Canadian-born Indigenous children, the majority of whom were identified as First Nations (67%) or Inuit (30%). The reported case rate in all Indigenous children was 8.6/100 000/year with the highest rate being in Inuit children (54.3/100 000/year) (table 2).

Forty-three (22%) of reported cases were in Canadian-born non-Indigenous children. Thirty children (15%) were born outside of Canada of whom 13 (43%) were born in sub-Saharan Africa. Among the foreign-born, Africa was the most common continent, and the Philippines and India were the most common countries of birth (table 1). The rates of reported cases for foreign-born and Canadian-born children with at least one foreign-born parent were 2.7 and 1.4 per 100 000, respectively. Of Canadian-born non-Indigenous children, 14 (26%) travelled to an endemic country.

Most cases resided in Manitoba (n=62, 31%) followed by Ontario (n=32, 16%), Québec (n=28, 14%) and Nunavut (n=28, 14%). Annual incidence rates by province or territory of residence and First Nation and Inuit status are shown in table 2. The highest rates were in Nunavut (80.6 cases per 100 000, greater than 80 times that of the rest of Canada combined) and Manitoba (8.5 cases per 100 000). Of the 70 children identified as First Nations, 64 (91%) had their residence on reserve.¹²

Results related to exposure and previous TB diagnosis are shown in table 3. A source case was identified in 73% of cases: most (n=91, 65%) were close household contacts of either a first-degree (48%) or second-degree (37%) relative. Twenty-five children (of whom 12 (48%) were First Nation and 9 (36%) were Inuit) had previously received TB treatment, chiefly for latent TB infection.

Selected clinical features are shown in table 4. TB was intrathoracic in 183 (92%) patients of whom 25 (14%) had extrathoracic involvement. The most common extrathoracic sites were the central nervous system (CNS) and peripheral lymph nodes. Miliary or disseminated disease was seen in 20 cases. Five (14%) cases in Inuit children involved the CNS, of whom 3 (60%) had received BCG vaccine. Approximately two-thirds had symptoms, most commonly cough fever and weight loss. Only 12 (6%) children with incident TB had the classic triad of cough, weight loss and night sweats and fewer than 5 children had haemoptysis.

One hundred and sixty-five children had at least one tuberculin skin test performed of which 144 (87%) were positive. An interferon gamma release assay test was performed in 13 children of whom 10 (77%) were positive. Overall, 80 (40%) children had at least one positive culture from any site. One hundred and forty-four children had at least one respiratory sample taken for mycobacterial

	Number (n)	%
Age (N=200)		
<1	28	14
1 to 4	82	41
5 to 9	36	18
10+	54	27
Sex (N=196)		
Male	99	50.5
Female	97	49.5
Ethnicity (N=200)		
Canadian born, Non-Indigenous	43	21.50
Canadian born, Indigenous, total	116	58
Canadian born, First Nations	(78)	(39)
Canadian born, Inuit	(35)	(17.5)
Canadian born, other	<5	n/a
Canadian born, Not Specified	11	5.5
Non-Canadian born, total (country or region of birth)	30	15
Africa	(13)	(6.5)
Philippines	(10)	(5)
South Asia	(5)	(2.5)
Other	<5	n/a

Table 2 Rates of reported case rates by province or territory of residence and Indigenous status

	Rate per 100 000	0–14 Population size	Cases (n)
Canada (N=200)			
Canada (N=200)	1.2	5 778 929	200
Province/territory of residence			
British Columbia	0.4	691 495	8
Alberta	0.9	764 638	21
Saskatchewan	3.1	213 796	20
Manitoba	8.5	243 534	62
Ontario	0.5	2 221 986	32
Québec	0.7	1 273 093	28
Atlantic Provinces*	n/a	343 482	<5
Nunavut	80.6	11 582	28
Indigenous status†			
Indigenous overall	8.6	448 865	116
First Nations overall	9.1	285 825	78
First Nations on-reserve	20.2	105 445	64
Inuit	54.3	21 495	35
Other	0.8	n/a	<5
Non-Indigenous	0.5	5 368 180	84

*Includes Newfoundland and Labrador, Prince Edward Island, Nova Scotia and New Brunswick. Fewer than five cases reported so incidence rate not calculated.

†Canada and province/territory-specific populations are averaged from 2013 to 2016 StatsCan July 1 yearly population estimates. Indigenous Status-specific populations are taken from the 2016 StatsCan Census.

culture; culture was positive in 31 of 77 (40%) sputum and 31 of 74 (42%) gastric aspirate samples; 55% of children with intrathoracic TB in whom a respiratory sample was obtained had negative cultures. Nineteen of 77 (25%) sputa were in those younger than 5 years; of these, fewer than 5 were culture positive.

Resistance to at least one drug was reported in 5 (7%) isolates. Most were resistant to isoniazid and rifampin and thus classified as multi-drug resistant. There were no proven cases of extensively-drug-resistant TB.

The median duration of treatment for all cases was 26 weeks (IQR 24–32), for TB meningitis 48 weeks (IQR 30–65) and for disseminated disease 48 weeks (IQR 40.5–54). Median duration of therapy for the five cases with documented resistance was 48 weeks (IQR 36–48). Most children were treated with a three-drug regimen of isoniazid, rifampicin and pyrazinamide (n=99, 50%) or four-drug regimen that included ethambutol (n=79, 40%). Use of directly observed therapy was reported in 183 (96%) cases for which this information was available.

Reported and minimum estimated rates of selected clinical events are shown in online supplemental table 1. Fifty-one per cent of children were admitted to hospital for a median of 14 days (IQR 7–19, maximum 252). Intensive care unit (ICU) admission status was known for 84 children of whom 11 (5.5%) required ICU level care. Seven (54%) children admitted to ICU had CNS involvement.

In 17 cases (9%), an ADR required a change in treatment and 6 cases required hospitalisation for the ADR. The most common drugs implicated in ADR were pyrazinamide (5%, most commonly for hepatotoxicity) and isoniazid (3%, most commonly for hepatotoxicity). Other implicated drugs included amikacin (hearing loss), rifampicin (hepatotoxicity), ethambutol (visual changes), linezolid (marrow suppression) and cycloserine (neuropathy).

Longer term follow-up information was provided in 106 cases and of these, 97% and 90% had shown clinical and radiologic improvement, respectively, at the time of final follow-up. Sixteen cases reported an extension of therapy beyond the originally planned time frame. Most common reasons for extended treatment included poor adherence to therapy (n=5), extrathoracic site of infection found

Table 3 Key exposure, epidemiologic and past tuberculosis history data

	Number (n)	%
Source case (N=198)		
Known	145	73
Unknown	53	27
Source case relationship (N=128)		
First-degree relative	62	48
Second-degree relative	47	37
Friend	11	9
Other	8	6
Exposure type (N=140)		
Close household	91	65
Close non-household	34	24
Casual	6	4
Visit to endemic country	7	5
Community/other	<5	n/a
Source case case known resistance to first-line agents* (N=137)		
Resistant	5	4
Not resistant	117	85
Not done or unknown	15	11
BCG vaccination (N=188)		
Yes†	86	46
No	81	43
Unknown	21	11
Previous tuberculosis diagnoses or treatment		
Latent tuberculosis, treated	17	8.5
Latent tuberculosis, untreated	<5	n/a
Active tuberculosis, treated	<5	n/a
Window prophylaxis	<5	n/a
Unspecified/unknown anti-tuberculosis therapy	<5	n/a

*All positive tuberculosis cultures in Canada undergo phenotypic drug-susceptibility testing. First-line agents are isoniazid, rifampin, pyrazinamide and ethambutol.

†For all children for whom immunisation status was known, BCG was received by 79% of Inuit children, 65% of First Nations children and 87% of foreign-born children.

after initiation of therapy (<5), poor radiologic or clinical response (<5) and drug resistance (<5). Fewer than five cases were reported as lost to follow-up and there were no TB-related deaths.

To understand the representativeness of our cases, we compared our results to the numbers of cases reported to the PHAC during the study time frame. Cases are de-identified in both reporting systems and could not be matched. For 2014 and 2015, where reporting periods were identical, CPSP reports were 74% of all cases reported to PHAC and 90% of PHAC reported cases when the province of Québec was excluded (online supplemental table 2). During the study, there were significant TB outbreaks in Nunavik, Québec, an Inuit region where TB is managed by clinicians not included in the CPSP surveillance system.¹³ Using additional demographic data from the province of Québec via PHAC (online supplemental table 3), we estimated a maximum number of 269 cases of childhood TB in Canada over the study period.¹⁴ Using these data, the minimum national incidence rates were 10.2/100 000/year for all Indigenous children, 100.8/100 000/year for Inuit children and 1.55/100 000/year for all children in Canada (online supplemental table 4).

DISCUSSION

This study is one of the first nation-wide surveys to collect TB data directly from treating clinicians. The overall rate of reported cases of childhood TB in this study was 1.2 per 100 000. This compares

Table 4 Selected clinical features and results of investigations

	Number (n), n (%)	Duration, median (IQR)
Disease site*		
Only intrathoracic	158 (81)	
Intrathoracic and extrathoracic	25 (13)	
Only extrathoracic	13 (7)	
Extrathoracic sites		
Central nervous system	16 (8)	
Peripheral lymph nodes	13 (7)	
Symptoms†		
Cough	84 (42)	28 days (14–30 days)
Fever	52 (26)	16 days (7–78 days)
Weight loss	36 (18)	
Haemoptysis	<5	
No recorded symptoms	65 (33)	
Tests of infection		
TST positive	144/165 (87)	
IGRA positive	10/13 (77)	
Positive TB culture		
Any site (one or more)	80/200 (40)	
Sputum	31/77 (40)	
Gastric aspirates	31/74 (42)	

* Four cases with incomplete data excluded from analysis of disease site.

† No data on presence or absence of symptoms for 18 cases.

IGRA, Interferon gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

with an approximate incidence of rate of 1.6/100 000 from PHAC data¹⁵ and 1.9 in the Netherlands,¹⁶ 2.0 in the UK¹⁷ and 0.7 per 100 000 in the USA.¹⁸

There was wide variation across Canada geographically and by population origin of the cases. The most striking finding is the burden of TB in Indigenous children. In 2016, Indigenous people comprised 19% of all reported TB cases in all ages.¹⁵ Though Indigenous children accounted for less than 10% of Canada's childhood population, 58% of reported TB was in this group. The rates in First Nations children (9.1 per 100 000 calculated from CPSP reported cases), especially those residing on reserve (20.2 per 100 000) are the drivers for childhood TB in the provinces of Manitoba, which had the greatest absolute number of cases, and Saskatchewan. The rate in Inuit children (54.3/100 000 population) is similar to reported childhood TB rates in high TB burden international settings.¹ Furthermore, when Québec cases not reported to CPSP are included, the minimum incidence rate in Inuit children is likely greater than 100/100 000 per year. Additionally, five cases from Newfoundland and Labrador where 90% of PHAC reported cases are Inuit were reported to PHAC but not to the CPSP.

In recognition of this hugely disproportionate burden in Inuit peoples, there has been a recent focus by the national representative organisation of Inuit peoples (Inuit Tapiriit Kanatami) and the Federal Government on social determinants of health and access to care as major contributors to TB in Inuit peoples¹⁸ and a pledge to reduce rates in Inuit Nunangat (the traditional territory of Inuit peoples in Canada) by 2030.¹⁹ A similar strategy and monitoring programme has been implemented by the Assembly of First Nations to focus on TB on First Nation reserves.¹⁹ The disproportionate burden of TB in Indigenous people in Canada has origins in the social determinants of health, historical trauma, the residential school system and racism within the healthcare system.²⁰ Reducing and eliminating TB in Indigenous communities through Indigenous-led and community-relevant approaches are the most urgent priorities for achieving elimination of childhood TB in Canada.

In keeping with other studies, most cases occurred in children under 5 years of age, reflecting the unique vulnerability of

young children to TB.²¹ There was a known TB contact in 82% of Canadian-born children, reinforcing the importance of contact tracing and a public health infrastructure to diagnose and prevent TB in Canada. Only 18% of foreign-born children had a known contact; most of them likely acquired TB infection in the country of birth or by travel to a higher TB endemic country after arrival in Canada.

Presenting symptoms were non-specific but most children were symptomatic for more than 2 weeks. Haemoptysis and the classic triad of weight loss, fever and night sweats was uncommon. This study highlights acuity and health system costs of childhood TB. About half of children were hospitalised and 5.5% were known to be admitted to ICU. TB meningitis, a condition associated with poor outcomes²² was the most common extrapulmonary site occurring in 8% of cases overall and 14% of reported disease in Inuit children. Of the children with meningitis with known BCG status, 7 (54%) had received the BCG vaccine.

A strength of this study was inclusion of clinicians managing cases through a cross-Canada collaborative network. While monthly surveys of clinicians are labour-intensive, it is possible to obtain rich epidemiologic and clinical data that is not possible through public health reporting. However, it has several limitations including voluntary reporting with some cases not captured. The largest discrepancy between the reported number of CPSP and PHAC cases was in Québec. Due to under-reporting, the representativeness of the acuity of cases cannot be confirmed, though minimum rates have been estimated. Follow-up data was less well reported than the initial incident case. Reasons for missing follow-up data included the reporting physician was not the physician who provided longer term care, the physician did not consent to being recontacted or the physician did not respond. Due to CPSP privacy rules, results with size <5 cannot be shown, which limits the description of rare outcomes. We captured region of residence and of diagnosis, however, these may not reflect the region of disease acquisition. We are not able to determine which cases were identified via a symptomatic child presenting to care versus via contact tracing nor were we able to determine clinical details of prior TB infection. Our surveillance asked only which drugs TB isolates were resistant to, not all drugs tested. The determination of TB acquired during travel used dates of travel to an endemic country, contact history and onset of disease, however, infection may have been acquired at another time. We recommend that future national surveillance and statistics about childhood TB should include detailed data about indigenous status, source case characteristics, prior infection and travel.

CONCLUSION

This surveillance study identified 200 incident cases of childhood TB over 3 years. Acuity of illness and resource utilisation were high. Most cases had a known source case. Outbreaks of childhood TB in low TB burden countries are best prevented by prompt identification of source cases, and evaluation and treatment of their contacts and require a well-functioning public health infrastructure and good contact tracing. Key geographies and groups have very high incidence rates of childhood TB that are comparable with highly endemic countries. Strong community and public health engagement are required to reduce disparities and achieve elimination of childhood TB in Canada.

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REFERENCES

- 1 WHO. Global tuberculosis report 2020. Geneva: World Health Organization, 2020. https://www.who.int/tb/publications/global_report/TB20_Exec_Sum_20201014.pdf
- 2 Laffeniere M, Hussain H, He N. Tuberculosis in Canada. *Lancet* 1946;1:585.
- 3 Canadian-Tuberculosis-Standards-7Th-Edition @ Www.Canada.Ca. Available: <https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition.html>
- 4 Kitai I, Morris SK, Kordy F, Lam R. diagnosis and management of pediatric tuberculosis in Canada. *CMAJ* 2017;189:E11–16.
- 5 Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med Overseas Ed* 2012;367:348–61.
- 6 Graham SM, Sismanidis C, Menzies HJ, et al. Importance of tuberculosis control to address child survival. *Lancet* 2014;383:1605–7.
- 7 Reuter A, Hughes J, Furin J. Challenges and controversies in childhood tuberculosis. *Lancet* 2019;394:967–78.
- 8 Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. proposed clinical case definitions for classification of intrathoracic tuberculosis disease. consensus from an expert panel. *J Infect Dis* 2012;205 Suppl 2:S199–208.
- 9 Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical case definitions for classification of intrathoracic tuberculosis in children: an update. *Clin Infect Dis* 2015;61:S179–87.
- 10 Statistics Canada. Population estimates on July 1st, by age and sex [Internet], 2018. Available: <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501&pickMembers%5B0%5D=1.15&pickMembers%5B1%5D=2.1> [Accessed 15 May 2019].
- 11 Statistics Canada. Aboriginal Population Profile, 2016 Census [Internet], 2016. Available: https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/abpopprof/details/page.cfm?Lang=E&Geo1=PR&Co-de1=01&Data=Count&SearchText=Canada&SearchType=Begins&B1=All&C1=All&SEX_ID=1&AGE_ID=2®SEO_ID=2 [Accessed 30 Aug 2019].
- 12 Government of Canada. Treaties and agreements [Internet], 2018. Available: <https://www.rcaanc-cirnac.gc.ca/eng/1100100028574/1529354437231> [Accessed 24 Mar 2020].
- 13 Dion R, Brisson M, Proulx JF, et al. Results of a population screening intervention for tuberculosis in a Nunavik village, Quebec, 2015–2016. *Can Commun Dis Rep* 2018;44:257–63.
- 14 Canadian Tuberculosis Reporting System Data Request - CTBRS 2018/2017 case and outcome data. Ottawa.
- 15 Vachon J, Gallant V, Siu W. Tuberculosis in Canada, 2016. *Can Commun Dis Rep* 2018;44:75–81.
- 16 Erkens CGM, de Vries G, Keizer ST, et al. The epidemiology of childhood tuberculosis in the Netherlands: still room for prevention. *BMC Infect Dis* 2014;14:295.
- 17 Mohiyuddin T, Seddon JA, Thomas HL, et al. The changing landscape of childhood tuberculosis in the United Kingdom: a retrospective cohort (2000–2015). *Pediatr Infect Dis J* 2019;38:470–5.
- 18 Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2017 [Internet], 2018. Available: <https://www.cdc.gov/tb/statistics/reports/2017/table4.htm>
- 19 Assembly of First Nations. Tuberculosis (TB) [Internet], 2019. Available: <http://www.afn.ca/tuberculosis-tb/> [Accessed 16 Jun 2021].
- 20 Jetty R. Tuberculosis among First Nations, Inuit and Métis children and youth in Canada: Beyond medical management [Internet]. *Pediatrics and Child Health*, 2020. Available: <https://www.cps.ca/en/documents/position/tuberculosis-among-first-nations-inuit-and-metis-children-and-youth#ref6> [Accessed 16 Jun 2021].
- 21 Marais BJ, Graham SM, Maeurer M, et al. Progress and challenges in childhood tuberculosis. *Lancet Infect Dis* 2013;13:287–9.
- 22 Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014;14:947–57.

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Vídeos de smartphones para prever a gravidade da apneia obstrutiva do sono

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RESUMO

Objetivo O diagnóstico da apneia obstrutiva do sono (AOS) é realizado através de polissonografia noturna (PSG). Dada a disponibilidade generalizada da tecnologia de vídeo smartphone, o nosso objetivo foi desenvolver e testar um sistema de pontuação padronizado para vídeos de smartphone e comparar estas pontuações com os resultados da PSG.

Métodos Foram incluídas crianças com idades compreendidas entre os 1-16 anos de idade submetidas a PSG devido a suspeita de AOS. Foi pedido aos pais que fizessem vídeos de 1-2 minutos da respiração com a qual estavam preocupados. Os vídeos foram classificados usando uma ferramenta recentemente desenvolvida e testada em cinco componentes: ruídos obstrutivos inspiratórios (1-4), presença de eventos obstrutivos (0-1), aumento do trabalho respiratório (0-1), respiração bucal (0-1) e extensão do pescoço (0-1). As pontuações do vídeo e o Índice de Hipopneia da Apneia Obstrutiva (IHAO) foram comparados utilizando a correlação de Spearman. Sensibilidade, especificidade, valor preditivo positivo e valor preditivo negativo foram calculados para diferentes pontuações de corte de modo a obter os melhores resultados.

Resultados Foram incluídos vídeos de 43 crianças (28 rapazes (65,1%), idade média de 5,7 anos (intervalo 2,6-14,0 anos), IHAO mediano de 3,8/hora (intervalo 0-82 eventos/hora). Nove crianças (20,9%) obtiveram uma pontuação de vídeo <3, todas com um IHAO ≤5 eventos/hora. Para uma pontuação de vídeo ≥3, a sensibilidade foi de 100%; a especificidade foi de 36%; o valor preditivo positivo foi de 53%; o valor preditivo negativo foi de 100% para a AOS moderada a grave (IHAO >5 eventos/hora).

Conclusão Desenvolvemos e validamos uma ferramenta clínica simples (a Pontuação de Vídeo de Apneia Obstrutiva do Sono Monash) para quantificar anomalias na respiração observadas em gravações de vídeo curtas realizadas em smartphone. Uma pontuação baixa exclui AOS moderada e grave e pode ser valiosa na triagem de crianças com sintomas de AOS.

INTRODUCTION

Obstructive sleep apnoea (OSA) affects up to 5.7% of children.¹ OSA is associated with sleep fragmentation and/or recurrent desaturation, which can have many negative health effects,² including impairments in behaviour and cognition and increased blood pressure.³⁻⁵ The current gold standard for diagnosis of OSA is polysomnography (PSG).¹ Overnight PSG is a limited resource⁶ and can be challenging to undertake in young children. Reliable alternatives to PSG have the potential to improve the timely diagnosis and treatment of children with OSA symptoms.

More than 80% of the Australian, US and UK populations have access to a smartphone.⁷⁻⁹ Smartphones can record high-definition video under low light conditions. Increasingly, parents bring smartphone videos to specialist clinics to illustrate their concerns regarding their child's breathing during sleep. Only one study has previously examined the use of videos to predict the severity of OSA in children¹⁰ using a scoring system for 30 min home video recordings that assessed the volume of inspiratory noises, type of inspiratory noise, movements during sleep, number of waking episodes, number of apnoeas, chest retractions and mouth breathing. The

What is already known on this topic?

- Symptoms of obstructive sleep apnoea affect many children but formal diagnosis requires overnight polysomnography in a sleep laboratory.
- Thirty-minute home video recordings have a high sensitivity but poor specificity for the presence of obstructive sleep apnoea (OSA) as defined by polysomnography.

What this study adds?

- Our study is the first study to examine the utility of short smartphone videos to aid in the diagnosis of OSA. We present a simple clinical tool to quantify signs of obstructed breathing during sleep in children as seen on short video recordings made on a smartphone. A low Monash Obstructive Sleep Apnoea Video Score rules out moderate to severe OSA.
- The Monash Obstructive Sleep Apnoea Score may be valuable in the triage of children with obstructive sleep-disordered breathing.

score was compared with PSG findings and had a sensitivity of 94% and a specificity of 68%. Although this result was promising, this technology is now outdated and the duration of recording is impractical for use in a routine outpatient setting. Much shorter videos taken on a smartphone may be helpful for primary care physicians, otolaryngologists, paediatricians and sleep medicine practitioners if they could be shown to reliably predict the results of PSG.

The aim of this study was to develop a standardised scoring system for short smartphone videos and to test if that score predicted the results obtained from overnight PSG, the current gold standard. We hypothesised that a standardised scoring system of smartphone video recordings would predict a PSG diagnosis of OSA.

MATERIALS AND METHODOLOGY

Development of the scoring tool

We devised a video scoring tool based on the previous home video-recording study.¹⁰ Several changes to the tool were then made in an iterative process of comparing the results between four scorers (two paediatric sleep physicians, one paediatric respiratory physician and one paediatric sleep medicine trainee) for four test videos and discussing points of difference. Correlation analysis was then undertaken between three paediatric sleep physicians and one sleep medicine trainee scoring 16 videos, using a preliminary version of the scoring tool (online supplemental table 1). Individual question responses and the total score were assessed for inter-rater reliability using intraclass correlation



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Table 1 The Monash Obstructive Sleep Apnoea Video Score

Instructions	Possible scores
This scoring system is designed to quantify signs of obstructed breathing when viewed on a smartphone video recording taken in a child's home when the child is asleep. Parents are asked to take a video approximately 1 min in duration, taken when the child's breathing is typical of what they are concerned about. It should be a close up of the child's head and chest, exposing as much as possible, with no background noise and using as much light as possible. Please select the number corresponding to what can be observed on the video for each question.	
1. Inspiratory noises Please select the most severe noise heard during the recording—noting that obstructed breathing noises can be quiet if they are very severe Quiet unobstructed breathing  Severe obstructed noise breathing	1–4
2. Presence of obstructive events An obstructive event is an absence or reduction of airflow despite ongoing effort of breathing and terminated by a breakthrough gasp, obstructive noise and/or movement. ► Absent (0). ► Present (1).	0–1
3. Evidence of increased work of breathing Evidence of accessory muscle use, nasal flaring, significant indrawing and/or paradoxical respiratory movements ► Absent (0). ► Present (1).	0–1
4. Mouth breathing ► Absent (0). ► Present (1).	0–1
5. Neck extension ► Absent (0). ► Present (1).	0–1
Total score	/8

coefficients (ICCs), with a two-way, random-effects model with measures of absolute agreement. Two videos were considered by all raters to be too dark for adequate assessment, leaving 14 videos (seven female, median age 4 years, range 1–9 years, video duration range 00:20–02:43 min) to be scored. The original scoring tool had an ICC=0.74 (95% CI 0.54 to 0.87) demonstrating moderate reliability.¹¹ Analysis of each question highlighted a lower ICC for 'inspiratory noises', and so this was modified to a Likert-type scale to better capture the ordinal assessment of this symptom. The final scoring tool is shown in table 1. Repeat scoring by the original four raters had an ICC of 0.92 (95% CI 0.83 to 0.97), demonstrating excellent reliability.¹¹

Prospective validation of the scoring tool

Recruitment

To determine the required sample size, we conservatively considered a difference in proportions of OSA of 80% in the abnormal video group and 30% in the normal video group, giving a sample size estimate of 42 (14 normal video and 28 abnormal video) for power of 0.8 and confidence level of 0.95.

Typically developing children aged 1–16 years undergoing PSG for suspected OSA were eligible. Exclusion criteria were major medical comorbidities, non-English speaking parents or parents without an email address to use to submit the video.

Recruitment was from January 2016 to December 2019 and occurred in two phases. During the first phase to May 2019, recruitment occurred during sleep clinic consultations. However, due to both low recruitment numbers and the waiting time between clinic appointment and PSG having increased to 6 months, the protocol was altered. During the second phase, consecutive parents of eligible children were approached by phone in the week prior to their child's PSG. Following informed verbal consent, recruited families were asked to bring a short smartphone video on the night of the PSG.

Video collection

Parents were instructed to take a video on their smartphone of their child asleep that was approximately 1 min in duration and captured the breathing pattern that they were concerned about. Instructions included to try and obtain a close up of child's head and chest, exposing the chest as much as possible, with no background noise and as much background light as possible. The parents were asked to send the video to the research team by email. Videos were stored securely under individual deidentified codes.

Polysomnography

All children underwent attended overnight PSG performed in the sleep laboratory using a commercially available PSG system (Gael PSG; Compumedics, Melbourne, Australia). Recording included electroencephalograms (central, frontal and occipital), left and right electro-oculograms, mental-submental and left and right tibial electromyograms, ECG, body position, infrared video, respiratory effort (z-RIP belts; Pro-Tech Services, Mukilteo, Washington, USA), oxygen saturation (Masimo Radical set to 2s averaging time; Masimo Corporation, Irvine, California, USA) and transcutaneous carbon dioxide (Sentec AG, Therwil, Switzerland). PSGs were scored by sleep technologists using standard criteria.¹² The following respiratory indices were calculated from the PSG: Respiratory Disturbance Index, which included all respiratory events (central and obstructive); Obstructive Apnoea Hypopnoea Index (OAH), which included obstructive apnoeas and hypopnoeas and mixed apnoeas; and Central Apnoea Hypopnoea Index, which included central apnoeas and hypopnoeas. Severity of OSA was defined by the OAH as per internationally recognised thresholds: primary snoring ≤ 1 event/hour, mild OSA 1.1–5.0 events/hour and moderate–severe OSA >5 events/hour.¹³ Total sleep time (TST) was the time in minutes that the patient spent asleep. The Arousal Index was the total number of arousals from sleep per hour of TST.

Scoring the video

For the prospective study, the videos were scored by a single experienced paediatric sleep physician (MJD) blinded to the clinical history and PSG results (scoring tool table 1). The scorer's overall impression was also documented: normal, possible OSA or highly suggestive of OSA. Scoring each video took approximately 2 min, allowing for viewing of the video twice. Technically poor videos were excluded if a score for any of the five scoring criteria could not be given, for example, too dark, no sound or inadequate exposure (not enough of the child could be seen on the video), or if the PSG included less than 5 hours TST.

Data analysis

Data were analysed using SPSS Statistics for Windows V.25.0. Spearman correlations were performed between all the scored variables and OAH. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for different cut-off scores to identify the best cut-off video score for detecting moderate–severe OSA.

Ethics statements

Written informed consent was obtained from all DNBC participants prior to data collection. Children born into the cohort participated on their mother's consent until age 18 years. Participants could withdraw their data from the cohort at any time (currently <20 mothers and children).²⁹

RESULTS

During the first phase of recruitment, 17 children provided videos, but only nine videos could be used as 7 children did not go on to have a PSG and one video was too dark. During the second phase, 201 children were identified as eligible, of whom 160 (80%) could be contacted and gave verbal consent. Written consent on the night of PSG was provided by 115 (72%) families (14 cancelled PSG; 29 decided not to provide written consent; and 2 were deemed ineligible when further information came to light on the night of the PSG). However, only 50 videos were received (50/115=43%), of which 15 (30%) had to be excluded as the videos were of poor quality and one child did not tolerate EEG recordings and so was excluded for

Table 2 Demographic details of study participants, their video recordings and PSG results

Participant details (n=43)		Summary statistics
Gender (female)		15 (35)
Age (years) at PSG		5.7 (2.7–14.0)
Video recordings		
Duration	<1 min	19 (44)
	≥1 and <5 min	23 (53)
	≥5 min	1 (2)
Night-time recording		39 (91)
Good quality*		38 (88)
Polysomnography results		
RDI (events/hour)		4.9 (0.1–85.9)
OAH1 (events/hour)		3.8 (0–82)
CnAHI (events/hour)		1.6 (0–6)
Total Arousal Index (events/hour)		13.5 (8.5–28)

Summary statistics are presented as n (%) or median (range).

*In five cases, there was concern about assessment of work of breathing due to coverage, light and duration of video, but judged sufficient to enable a score to be applied.

CnAHI, Central Apnoea Hypopnoea Index; OAH1, Obstructive Apnoea Hypopnoea Index; PSG, polysomnography; RDI, Respiratory Disturbance Index.

inadequate PSG data. Therefore, videos for 43 children (a participation rate of 37%) were included in the analysis (table 2). There were 28 males (65.1%), and the median age was 5.7 years (range 2.6–14.0 years). The median OAH1 was 3.8 events/hour (range 0–82 events/hour), with 11 children (25.6%) having primary snoring, 14 (32.6%) mild OSA and 18 (41.9%) moderate–severe OSA.

The distribution of video score by PSG results is shown in figure 1. No child received the maximum score of 8. Different cut-off scores were explored to determine the best sensitivity and specificity. Nine children out of 43 (20.9%) had a score of <3, all of whom had an OAH1 of ≤5 events/hour (primary snoring–mild OSA). For a total video score of ≥3, the sensitivity was 100% (95% CI 82% to 100%); the specificity was 36% (95% CI 18% to 58%); the positive predictive value was 53% (95% CI 35% to 70%) and the negative predictive value was 100% (95% CI 66% to 100%) to predict moderate–severe OSA (OAH1 >5 events/hour) (area under the curve revealed poor overall reliability at 0.68). Three children had a high video score (5–7) but an OAH1 of <1 event/hour. The videos for these children were reviewed by the investigators and were confirmed to contain obstructed inspiratory sounds, increased work of breathing and the presence of obstructive events. Two of the three had no sleep in the supine position on the PSG, which may have resulted in an underestimation of the severity of OSA.

The extent to which the individual questions on the video score correlated with OAH1 was variable when assessed using Spearman's rho (table 3), with 'mouth breathing' having the weakest linear relationship, 'inspiratory noises' a moderately significant positive association and 'increased work of breathing' a weakly significant positive association. The 'overall impression of the scorer' also indicated a moderately significant positive association with OAH1 ($r_s(41)=0.42$, $p=0.005$) (table 3). An overall impression of 'highly suggestive of OSA' (n=15) had a very low positive predictive value of 53% for the presence of moderate–severe OSA. Conversely, and similarly to the performance of the video score, of the 10 children with an overall impression of 'normal' from the scoring clinician, 9 did not have moderate–severe OSA.

DISCUSSION

This is the first study investigating the relationship between short smartphone videos and the presence and severity of OSA confirmed by PSG in children. We have developed a standardised test instrument with a scoring system for videos that achieved excellent inter-rater reliability between paediatric sleep physicians. A score of ≥3 on this new tool had 100% sensitivity for the presence of moderate–severe OSA on PSG, but the specificity and positive predictive value of the score were low. A score below 3 therefore reliably rules out moderate–severe OSA in this population of children referred for PSG, but a higher score does

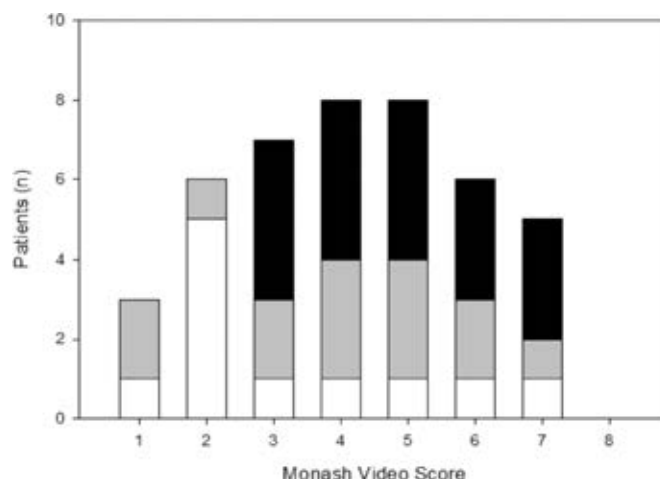


Figure 1 Distribution of Monash OSA Video Score by polysomnography results. White bars indicate OAH1 of <1/hour; grey bars indicate OAH1 of 1–4.9/hour; black bars indicate OAH1 of ≥5/hour. OAH1, Obstructive Apnoea Hypopnoea Index.

not confirm the diagnosis. Similarly, an overall impression of normal from the scoring clinician reliably ruled out moderate–severe OSA.

The majority of children with symptoms of obstructed breathing during sleep are referred to an otolaryngologist for assessment, with less than 10% of children having PSG prior to adenotonsillectomy (AT) in the USA,¹⁴ one of the countries with the highest availability of PSG.¹⁵ Recruitment for the largest randomised controlled trial of AT for OSA to date revealed that half of the children waiting for AT did not have OSA defined as an OAH1 of >2 events/hour.¹⁶ Observation for 6 months leads to equivalent improvement in the OAH1 as AT in children aged 2–4 years with mild–moderate OSA,¹⁷ and this would be expected to be true also for children with primary snoring. Therefore, a tool with a high negative predictive value, applicable to primary care or outpatient surgical settings, such as the video score presented here, has the potential to reduce referral for AT, especially when used in conjunction with a detailed clinical history of sleep-related symptoms.^{17,18}

The value of the video score in ruling out OSA depends on the validity of the OAH1 as a method for defining OSA. The utility of this single outcome measure from PSG to predict both the severity of symptoms and the benefit of surgery has been questioned for both adults¹⁹ and children.^{6,18} Despite this limitation, division of the condition into primary snoring/mild OSA compared with moderate/severe OSA (OAH1 >5 events/hour) is becoming widely recognised as a reasonable threshold for the indication of AT based on the results of randomised controlled trials.^{16,17} Given that symptoms of obstructive sleep-disordered breathing affect about 10% of children,²⁰ rationalising the use of both PSG and AT is helpful in allocating resources to those most likely to benefit.

We based the concept for this study on the only other report of video recordings used in this way in children, published in 1996.¹⁰ In that study, parents supplied a 30 min home video-recording for analysis, considerably longer than those used in our study, but despite the longer recording duration, our results show similar findings, with a high sensitivity but low specificity. Both methods rely on parents being able to take a good quality video of their child sleeping and our study introduced the extra step of transmitting a large video file electronically for analysis. Obtaining smartphone videos proved to be more difficult

Table 3 Spearman correlation of the scoring tool questions with the Obstructive Apnoea Hypopnoea Index from polysomnography

Variable	r_s	P value
Inspiratory noises	0.432	0.004
Obstructive events	0.246	0.11
Increased work of breathing	0.303	0.048
Mouth breathing	0.009	0.96
Neck extension	0.152	0.33
Overall impression	0.424	0.005

than we had anticipated, as evidenced by the large dropout rate (73%) from phone consent to completion of the study. Some parents who gave consent but did not provide a video reported being concerned about disturbing the child or having difficulty capturing the breathing pattern of concern for other reasons. The sleeping position of the child likely also contributed to discordance between the video findings and the result of the PSG. Parents are also most likely to record the video before they go to bed themselves (or during the day as in some younger children in our series), and therefore may not capture rapid eye movement (REM) sleep. OSA is often REM sleep-related in young children especially²¹ and may thus be concentrated in the latter half of the night. This mismatch of the timing of the video versus the timing of obstructive events is likely to lead to an underestimation of OSA by the video score. However, in fact, our findings showed the reverse—a number of children with a high video score despite primary snoring or mild OSA on PSG. This finding suggests that parents may be videoing events that concerned them (as per the instructions and as confirmed by the video scores), when these events may be rare, position dependent or variable night-to-night and not captured by the single night of PSG.

As mentioned previously, our study is limited by comparison of the video score only to OAH, the most common measurement of OSA severity used in assessment of alternative tools to PSG. Additional evidence for the tool's utility could be obtained by using a patient-centred outcome such as quality of life and the extent of improvement in that measure after AT, to determine whether the video score is a useful adjunct in determining children likely to benefit most from surgical treatment. Our single-site study was limited to children referred for PSG and used a group of clinicians working in the same department as scorers in development of the scoring tool, and repeating the study in primary care or a surgical outpatient setting would test its potential applicability to other populations of children and a wider range of scorers.

In summary, we have developed and validated a simple clinical tool to quantify abnormalities in breathing seen on short video recordings made on a smartphone. A low score on this tool rules out moderate to severe OSA and may be valuable in the triage of children otherwise referred for PSG. Future studies should determine the performance of this tool in other settings and in predicting benefit from AT as treatment of OSA.

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REFERENCES

- Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2012;130:576–84.
- Waters KA, Suresh S, Nixon GM. Sleep disorders in children. *Med J Aust* 2013;199:S31–5.
- Bourke R, Anderson V, Yang JSC, et al. Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. *Sleep Med* 2011;12:489–96.
- Horne RSC, Yang JSC, Walter LM, et al. Elevated blood pressure during sleep and wake in children with sleep-disordered breathing. *Pediatrics* 2011;128:e85–92.
- Biggs SN, Bourke R, Anderson V, et al. Working memory in children with sleep-disordered breathing: objective versus subjective measures. *Sleep Med* 2011;12:887–91.
- Nixon GM, Kubba H, Perrett KP. Time to open our eyes? a challenge to the role of polysomnography for trials in pediatric sleep-disordered breathing. *J Clin Sleep Med* 2018;14:489–90.
- Shott SR, Donnelly LF. Cine magnetic resonance imaging: evaluation of persistent airway obstruction after tonsil and adenoidectomy in children with Down syndrome. *Laryngoscope* 2004;114:1724–9.
- Anderson M, Cohn S. Mobile technology and home broadband 2019. Washington, D.C, USA: Pew Research Center, 2019. https://www.pewresearch.org/internet/wp-content/uploads/sites/9/2019/06/PI_2019.06.13_Mobile-Technology-and-Home-Broadband_FINAL2.pdf
- Lee P, Calugar-Pop C. Global mobile consumer survey: UK cut. Plateauing at the peak. The state of the smartphone. London, UK: Deloitte LLP, 2019. <https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/technology-media-telecommunications/deloitte-uk-plateauing-at-the-peak-the-state-of-the-smartphone.pdf>
- Sivan Y, Kornecki A, Schonfeld T. Screening obstructive sleep apnoea syndrome by home videotape recording in children. *Eur Respir J* 1996;9:2127–31.
- Dalton STP, Nixon GM, Horne RSC. Mobile phone video clips to aid diagnosis of OSA – development of a scoring tool. *J Sleep Res* 2018;27.
- Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. deliberations of the sleep apnea definitions Task force of the American Academy of sleep medicine. *J Clin Sleep Med* 2012;8:597–619.
- Katz ES, Greene MG, Carson KA, et al. Night-to-night variability of polysomnography in children with suspected obstructive sleep apnea. *J Pediatr* 2002;140:589–94.
- Roland PS, Rosenfeld RM, Brooks LJ, et al. Clinical practice guideline: polysomnography for sleep-disordered breathing prior to tonsillectomy in children. *Otolaryngol Head Neck Surg* 2011;145:S1–15.
- Marshall NS, Wilsom BR, McEvoy RD, et al. Polysomnography in Australia—trends in provision. *J Clin Sleep Med* 2007;3:281–4.
- Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med* 2013;368:2366–76.
- Fehm J, Nerfeldt P, Browaldh N, et al. Effectiveness of adenotonsillectomy vs watchful waiting in young children with mild to moderate obstructive sleep apnea: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg* 2020;146:647.
- Rosen CL, Wang R, Taylor HG, et al. Utility of symptoms to predict treatment outcomes in obstructive sleep apnea syndrome. *Pediatrics* 2015;135:e662–71.
- Punjabi NM, Sorkin JD, Katzel LJ, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 2002;165:877–82.
- Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:242–52.
- Verginis N, Jolley D, Horne RSC, et al. Sleep state distribution of obstructive events in children: is obstructive sleep apnoea really a rapid eye movement sleep-related condition? *J Sleep Res* 2009;18:411–4.

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ARTIGO ORIGINAL

A sequenciação do ARN sanguíneo revela uma sobreposição da expressão genética entre domínios de fenótipo de DPOC

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RESUMO

Fundamentação A DPOC pode ser avaliada através de sistemas de classificação multidimensional com componentes de três domínios: testes de função pulmonar, sintomas e características sistêmicas. Clinicamente, as medidas podem ser usadas de forma intercambiável, embora não seja conhecido se partilham uma patobiologia similar.

Objetivo Utilizar a sequência de ARN (RNA-seq) para determinar se existe uma sobreposição nos mecanismos e consequências biológicas subjacentes a conduzir diferentes componentes dos sistemas de classificação multidimensional.

Métodos No estudo de Epidemiologia Genética da DPOC, foi recolhido sangue inteiro para a RNA-seq de fumadores atuais e ex-fumadores. Testámos a sobreposição na expressão genética e vias biológicas associadas ao estado de caso-controlo e aos fenótipos quantitativos da DPOC dentro e entre os três domínios.

Resultados Em 2647 indivíduos, verificaram-se 3030 genes diferentemente expressos em qualquer dos três domínios ou estado de caso-controlo. Cinco genes sobrepuaram-se entre os três domínios e o estado de caso-controlo, incluindo o receptor acoplado à proteína 15 (GPR15), a sestrina 1 (SESN1) e a proteína de ligação ao guanilato 1 induzida por interferão (GBP1), que foram associados ao declínio longitudinal da FEV1. A sobreposição entre os três domínios foi enriquecida para as vias relacionadas com os componentes celulares.

Conclusões Identificámos conjuntos de genes e vias que se sobrepõem entre 12 fenótipos relacionados com a DPOC e o estado de caso-controlo. Não se registaram vias representadas na sobreposição entre os três domínios e o estado de caso-controlo, mas identificámos múltiplos genes que demonstraram um padrão de expressão consistente em vários dos fenótipos. Os padrões de correlação da expressão dos genes foram no geral semelhantes à correlação dos fenótipos clínicos nos domínios de TFP e sintomas, mas não às características sistêmicas.

BACKGROUND

The assessment of severity in COPD has evolved dramatically over the last several decades. While COPD severity was initially characterised by the degree of airflow obstruction based on FEV₁, with arbitrary thresholds to define severe disease, multidimensional grading systems have since been incorporated into clinical care.¹ The components of the multidimensional grading systems broadly fall into three categories: pulmonary function tests (PFTs), symptom evaluations and systemic features. While many of the measures are used complementarily,² it is unknown if there exists a similar overlap in the genetics and biological pathways that underlie the observed phenotypes.

Gene expression microarrays and RNA sequencing (RNA-seq) in multiple tissues have been used to identify and characterise COPD. In addition, differentially expressed genes and pathways have been shown to overlap across matched disease-associated tissue types in COPD.³ Accordingly, blood RNA-seq has been used as a proxy to identify differential gene expression in multiple COPD-related phenotypes.^{4–6} However, several clinically relevant phenotypes, including those used in multidimensional grading systems, have not been explored using RNA-seq.

Key messages

What is the key question?

► Can we use RNA sequencing to identify overlap in the biological mechanisms underlying multiple COPD-related phenotypes used to assess clinical severity of COPD?

What is the bottom line?

► There are five genes that overlap between several phenotypes and are associated with disease progression.

Why read on?

► We present the results of the largest sample size in a COPD gene expression study and demonstrate a unique set of genes overlapped between multiple clinically relevant phenotypes that is also associated with disease progression.

We hypothesised that the three domains (symptoms, PFTs and systemic features) of multidimensional grading systems used clinically to assess disease severity would have overlapping gene expression profiles. Furthermore, we investigated how gene expression from these three domains overlap with gene expression in COPD cases versus controls to enrich for associated genes in the context of COPD. We analysed overlapping gene expression profiles and pathways associated with 12 phenotypes, chosen for their role in clinical practice and in multidimensional grading systems, from the Genetic Epidemiology of COPD (COPDGene) study. The traits of interest include FEV₁, FVC, FEV₁:FVC ratio, diffusion capacity of carbon monoxide (DLCO), Body Mass Index (BMI), 6 min walk distance (6MWD), resting arterial oxygen saturation (SaO₂), haemoglobin (Hgb) concentration, Modified Medical Research Council (MMRC) Dyspnoea Scale, St. George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and presence or absence of chronic bronchitis. In addition, we tested the association of genes identified cross-sectionally with longitudinal changes in disease severity. By exploring the biology common to the components of multidimensional grading systems, we sought to build a foundation to understand mechanisms underlying COPD heterogeneity, which may inform diagnosis, prognosis and treatment.

METHODS

Subjects

The COPDGene study is a longitudinal, multicentre observational study designed to identify genetic factors associated with COPD.⁷ Subjects had a history of smoking of at least 10 pack-years and were 45–80 years old at the time of enrolment. Subjects participated in follow-up visits of 5 and 10 years. Additional

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details regarding study protocol, inclusion criteria and data collection forms are available online (www.copdgene.org).

Data collection

Study subjects completed multiple questionnaires, including MMRC Dyspnoea Scale, SGRQ and CAT. Subjects completed a standard spirometry protocol before and after inhaled albuterol, DLCO and 6MWD. Other parameters assessed include BMI, SaO₂ via pulse oximetry and Hgb.

RNA sequencing

A subset of subjects who participated in the 5-year follow-up visit had whole blood collected in a PaxGene RNA tube. Total RNA was extracted and sequenced on an Illumina HiSeq. Details of RNA-seq methods have been published.⁸

Case definitions

COPD was defined as post-bronchodilator FEV₁ to FVC ratio of <0.70 and FEV₁ <80% predicted, corresponding to the Global Initiative for Obstructive Lung Disease (GOLD) spirometry grades 2–4. Control subjects were defined as postbronchodilator ratio of ≥0.70 and FEV₁ ≥80% predicted, previously termed GOLD 0 in COPDgene.⁹ The PFT domain included postbronchodilator measures of FEV₁ % predicted, FVC % predicted, FEV₁:FVC ratio and DLCO % predicted. The symptom domain included SGRQ total score, MMRC score, CAT score and presence of chronic bronchitis by the ATS/ERS definition.^{10,11} The systemic domain included 6MWD, BMI, SaO₂ and Hgb. We defined overlapping gene sets by the intersection of differential expression results across phenotypes within each domain, which were then intersected across the different domains. We intersected these results with COPD case–control status to determine disease relevance.

Statistical analysis

Prior to analysis, genes with fewer than one count per million in more than 50% of the sample size were excluded. Differential gene expression was performed using the R/Bioconductor packages limma and voom,¹² where the associations between transcript expression levels and the pulmonary function, symptom and systemic phenotypes were tested. With the exceptions of case–control status and presence or absence of chronic bronchitis, all outcomes were considered as quantitative traits. Models were adjusted for clinical covariates previously shown to affect gene expression, as well as white blood cell percentages, as summarised in online supplemental table 1 in the online data supplement.^{8,13,14} Surrogate variables used to estimate other latent effects were included in all models as covariates, using the sva package.¹⁵ Multiple testing was controlled for false discovery rate (FDR) <5%. Venn diagrams were performed using the VennDiagram package.¹⁶ Pathway analysis was conducted using the Database for Annotation, Visualisation, and Integrated Discovery Functional Annotation Tool.¹⁷ Spearman correlation matrices between the clinical outcomes and between the adjusted log fold changes of differentially expressed genes in each clinical outcome were visualised using heatmaps created using the ggplot2 package.¹⁸

RESULTS

Subject characteristics

The COPDgene study included 10 198 subjects with a history of current or former smoking. Whole-blood RNA-seq was available on 2647 subjects who attended a 5-year follow-up visit (table 1). The average age was 65 years with a slight predominance of male subjects. Three-quarters of the subjects were non-Hispanic white, and one-quarter were African–American. Study subjects were mostly former smokers, with 35.7% of the subjects as current smokers at the time of the study visit.

Differential gene expression and pathway analysis

Subjects were excluded from an analysis if they were missing data on the phenotype of interest or model covariates (online supplemental table 1). Differential gene expression analysis was performed for 12 clinical phenotypes as well as COPD case–control status. There were 3030 genes that were differentially expressed (FDR <5%) in any of the three categories—PFT (564 genes), symptoms (376) or systemic effects (2560)—or case–control status (135) (figure 1 and online supplemental tables 2–14). FEV₁, SGRQ and BMI had the most differentially expressed genes in their respective domains, contributing the most

Table 1 Phase II RNA sequencing subject characteristics

Characteristics	Mean (SD) or n (%)
n	2647
Age (years)	65.5 (8.6)
Male sex	1366 (51.6)
Non-Hispanic white	1980 (74.8)
African–American	667 (25.2)
Current smoker	941 (35.7)
Smoking pack-years	44.1 (23.9)
GOLD stage	
PRISm	331 (12.7)
Normal spirometry	1128 (43.4)
GOLD 1	258 (9.9)
GOLD 2	522 (20.1)
GOLD 3	254 (9.8)
GOLD 4	105 (4.0)
FEV ₁ % predicted, postbronchodilator	78.5 (24.2)
FEV ₁ :FVC ratio, postbronchodilator	0.68 (0.15)
FVC % predicted, postbronchodilator	87.0 (17.6)
DLCO % predicted	78.2 (22.3)
BMI (kg/m ²)	29.0 (6.3)
Haemoglobin (mg/dL)	13.9 (1.5)
Resting SaO ₂ (%)	96.1 (2.7)
6 min walk distance (ft)	1310.9 (440.4)
SGRQ total score	22.1 (20.4)
MMRC dyspnoea score	1.2 (1.4)
COPD Assessment Test	11.4 (8.3)

Data presented as mean (SD) or %.

BMI, Body Mass Index; DLCO, diffusing capacity of carbon monoxide; GOLD, Global Initiative for Obstructive Lung Disease; MMRC, Modified Medical Research Council; PRISm, preserved ratio impaired spirometry; SaO₂, arterial saturation of oxygen; SGRQ, St. George's Respiratory Questionnaire.

information to the domain gene set. There were five genes that overlapped between the three categories and case–control status, including *G protein-coupled receptor 15* (*GPR15*), *sestrin 1* (*SESN1*), *interferon-induced guanylate-binding protein 1* (*GBP1*), *rearranged L-myc fusion* (*RLF*) and *hepatic leukaemia factor* (*HLF*) (table 2).

Increased *SESN1* expression was associated with less severe disease, demonstrated by positive associations with multiple PFT phenotypes and 6MWD, and negative associations with symptom scales and case–control status. *HLF* expression was similarly positively associated with one systemic phenotype (BMI) and one PFT phenotype (FEV₁:FVC ratio), with corresponding negative associations with symptom scores and COPD case–control status. Conversely, expression of *RLF*, *GBP1* and *GPR15* was associated with more severe disease. These genes had negative associations with systemic (except BMI) and PFT phenotypes and corresponding positive associations with symptom phenotypes and COPD case–control status.

There were 111 genes that overlapped between the three domains. The pathways represented by the genes in the overlap of the three domains included phosphoproteins, polymorphism and cytosol (table 3).

There were also 280 genes that overlapped between the PFT category and the systemic category, in contrast to 157 and 226 genes that overlapped between PFT and symptom categories and systemic and symptom categories, respectively. Within the PFT domain, there were 108 genes overlapping between FEV₁ and FVC and 120 genes overlapping between FEV₁ and FEV₁:FVC ratio (figure 1). There were only 14 genes overlapping across all three spirometry measures. Only two of these genes also overlapped with DLCO. The largest overlap in the symptom category was between SGRQ and CAT, consisting of 62 genes (figure 1), while there were only 28 genes that overlapped between SGRQ and MMRC. Within the symptom domain, there were

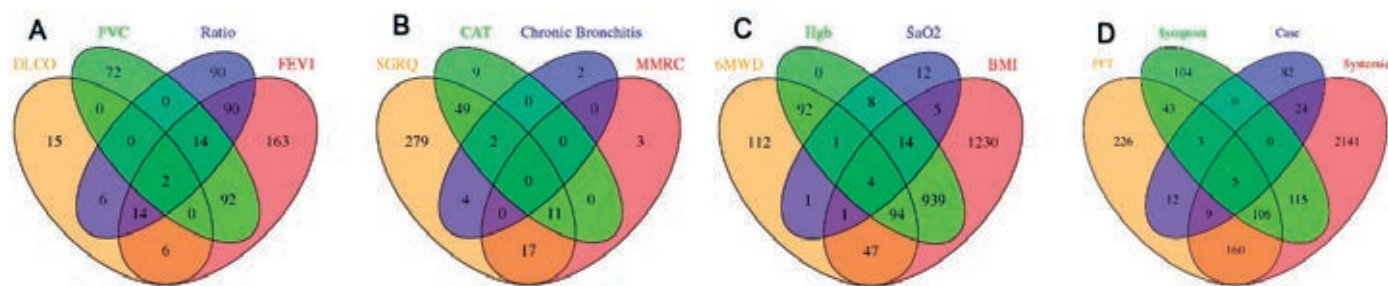


Figure 1 Venn diagrams of overlap of differential gene expression within PFTs (A), symptoms (B), systemic features (C) and between the three domains and COPD case–control status (D). PFTs include FEV₁, % predicted, FEV₁:FVC ratio, FVC % predicted and DLCO. Symptom measures include SGRQ, CAT, chronic bronchitis and MMRC. Systemic features include 6MWD, Hgb, SaO₂ and BMI. The numbers represent the number of genes in each overlapping or non-overlapping region of the Venn diagram. 6MWD, 6 min walk distance; BMI, Body Mass Index; CAT, COPD Assessment Test; DLCO, diffusion capacity of carbon monoxide; Hgb, haemoglobin; MMRC, Modified Medical Research Council; PFT, pulmonary function test; SaO₂, arterial oxygen saturation; SGRQ, St. George's Respiratory Questionnaire.

279 genes exclusively differentially expressed in the SGRQ phenotype, more than all the other phenotypes and overlaps combined. Chronic bronchitis had two genes that overlapped with CAT; no genes overlapped with MMRC; and only four genes overlapped with SGRQ. Within the systemic domain, there were 1152 genes differentially expressed in association with Hgb, yet there were no genes that were unique to Hgb (figure 1). The largest overlap between any two phenotypes in the three domains was between Hgb and BMI, with 1051 overlapped genes. There were 32 pathways over-represented by the genes overlapping between Hgb and BMI, including several cellular processes and components, as well as immune pathways, such as host–virus interaction (table 3).

Spearman correlations between the clinical variables (figure 2A) and the differential gene expression (figure 2B), quantified by the adjusted log fold changes, for each of the outcomes are shown in figure 2. Chronic bronchitis was not included, given binary variables are not suitable for this analysis. Among the clinical variables, the symptom measures were positively correlated with each other, as were the PFT measurements. As expected, the symptom scores and PFT variables were negatively correlated. The systemic measures were positively correlated with PFT measures and had a weak positive correlation with each other. There was mixed correlation between the symptom measures and systemic measures; SGRQ and CAT were weakly positively correlated with the systemic measures, while MMRC was negatively correlated with Hgb and resting SaO₂ and mildly positively correlated with BMI.

Similar to the clinical variables, the gene expressions in the symptom and PFT categories were positively correlated within each domain but negatively correlated across the two categories. In contrast, while the phenotypes in the systemic category were positively correlated, the gene expression within the systemic category were negatively correlated. In addition, resting SaO₂ and Hgb were negatively correlated with the symptom phenotypes, while BMI was positively correlated.

Longitudinal lung function decline

There were 960 subjects from the phase II RNA-seq subset who completed the phase III (10-year) follow-up visit (table 4). The subjects who completed the phase III visit had a higher proportion of female subjects and a lower proportion of current smokers. In addition, the phase III subjects were slightly younger on average than expected, such that the average age was under 5 years older than the 5-year follow-up cohort. We tested the five genes in table 2 for association with lung function decline, defined by change in FEV₁ % predicted. After adjusting for age, race, gender, smoking status, smoking pack-years and baseline FEV₁ % predicted, increased expressions of *GPR15*, *SESN1* and *GBP1* were associated with greater decline in FEV₁ % predicted at phase III (online supplemental table 15). There was no significant effect of *RLF* and *HLF* on change in FEV₁ % predicted at phase III.

DISCUSSION

Using whole-blood RNA-seq on 2647 subjects from the phase II visit of the COPD Gene Study, we identified unique gene sets for 12 different COPD-related phenotypes and case–control status as well as patterns

of overlap in differential gene expression and biological pathways represented by the gene sets. The genes over-represented in the overlap between the three domains and COPD case–control status represent diverse function, from altered expression due to smoking, to epigenetic regulation, inflammation and carcinogenesis, but demonstrate a consistent pattern of alteration across the phenotype domains. A subset of the overlapping genes was associated with decline in FEV₁ % predicted. While many of the associated pathways represent non-specific cellular components and cellular processes, there were multiple pathways related to immunity, specifically virus defence. In addition, we compared the correlation of the quantitative phenotypes to the correlation of the gene expression in the same phenotypes and found similar patterns in the symptom and PFT categories but a different pattern in the systemic domain. These findings grant important insights into some of the biological similarities that may be used to construct a biological assessment of COPD severity as well as biological differences that underlie the clinical heterogeneity of COPD.

There were five genes overlapping between the three phenotype domains and case–control status, with three genes associated with longitudinal decline in FEV₁ % predicted. *GPR15* encodes the surface membrane-bound GPR15, which serves as a chemokine receptor for HIV 1 and 2¹⁹ and has been implicated in the pathological movement of lymphocytes to the gut²⁰ and skin.²¹ In addition, *GPR15* has previously been identified as a smoking-related differentially expressed gene.⁸ Another prior study confirmed that while *GPR15* was associated with smoking, it was not associated with several lung diseases, including COPD.²² However, this study only included 20 subjects with COPD. Adjusted for smoking status, we found that increased *GPR15* expression was associated with increased symptom burden and case–control status and decline in FEV₁ % predicted, showing effects beyond cigarette smoking.

SESN1 belongs to a family of highly conserved stress-responsive proteins and has been shown to play a role in cellular protection from oxidative stress.²³ Transforming growth factor beta (TGF- β) has been previously associated with the development of COPD,²⁴ and sestrins have been implicated in the regulation of the TGF- β pathway.²⁵ We observed that increased expression of *SESN1* was associated with less severe disease across multiple phenotypes. However, increased *SESN1* expression was associated with greater decline in FEV₁ % predicted. This could suggest that *SESN1* plays a different role in the development and progression of COPD such that the role of *SESN1* may change over time. Further functional studies may help elucidate its role in pathogenesis versus prognostication.

GBP1 encodes for guanylate-binding protein 1, which is involved in cellular component and cell cycle pathways.²⁶ *GBP1* expression is strongly influenced by interferon- γ and has been implicated in the development of autoimmune diseases, including dermatomyositis.²⁷ We observed that increased *GBP1* expression was associated with case–control status, increased symptoms on SGRQ and longitudinal decline in FEV₁ % predicted. While we did not directly observe its effects, the association of *GBP1* could imply the involvement of interferon- γ in COPD, which has been previously associated with the development of emphysema in a murine model.²⁸

HLF is a basic leucine zipper transcription factor that has been implicated in the pathogenesis of metastases in non-small cell lung

Table 2 Log fold change and adjusted p values in each COPD-related phenotype and case-control status for overlapped genes

HGNC symbol		<i>SESNI</i>	<i>HLF</i>	<i>RLF</i>	<i>GBP1</i>	<i>GPR15</i>
Systemic domain	BMI logFC*	0.0027	0.011	–	–0.0044	–0.012
	P value	3.95E-03	6.48E-05		6.41E-05	4.40E-06
	Hgb logFC	0.012	–	–	0.0095	0.047
	P value	1.61E-03			4.90E-02	3.01E-05
	6MWD logFC	3.75E-05	–	–	–	–
	P value	0.041				
	SaO ₂ logFC	–	–	–0.007	–	–
	P value			7.73E-12		
Symptom domain	SGRQ logFC	–0.00099	–0.0025	0.00057	0.0012	0.0025
	P value	0.0018	0.033	0.00076	0.0012	0.012
	CAT logFC	–0.0023	–0.0073	–	–	–
	P value	0.011	0.014			
	MMRC logFC	–0.014	–	–	–	–
	P value	0.019				
	CB logFC	–	–	–	–	–
	P value					
PFT domain	FEV ₁ logFC	0.00079	–	–0.00065	–0.0012	–0.005
	P value	6.69E-03		5.76E-07	1.01E-04	2.87E-15
	FVC logFC	–	–	–0.00055	–	–0.0028
	P value			0.014		0.038
	Ratio logFC	0.16	0.65	–0.12	–0.26	–0.89
	P value	1.09E-03	6.42E-06	2.46E-07	1.14E-06	7.04E-16
	DLCO logFC	0.0014	–	–0.00052	–0.0017	–0.0058
	P value	6.20E-06		2.38E-02	3.63E-05	6.96E-12
Case-control status	COPD case-control logFC	–0.057	–0.19	0.047	0.122	0.32
	P value	2.19E-02	8.45E-04	4.14E-02	2.52E-02	3.46E-11

*Data presented as log₂ fold change per unit variable. P value adjusted for multiple testing. Empty cells are denoted by –, representing gene expression that did not meet 5% false discovery threshold.

BMI, Body Mass Index; CAT, COPD assessment test; CB, chronic bronchitis; DLCO, diffusing capacity of carbon monoxide; *GBP1*, guanylate-binding protein 1; *GPR15*, G protein-coupled receptor 15; Hgb, haemoglobin; *HLF*, hepatic leukaemia factor; MMRC, Modified Medical Research Council; 6MWD, 6 min walk distance; PFT, pulmonary function test; *RLF*, rearranged L-Myc fusion; SaO₂, arterial saturation of oxygen; *SESNI*, sestrin 1; SGRQ, St. George's Respiratory Questionnaire.

cancer.²⁹ *RLF* is an epigenetic modifier that has been shown to affect the methylation of numerous sites of transcriptional regulation,³⁰ but its effect on expression is subtle and its relevance to biological pathways remains unclear.

While prior studies have explored the gene expression of multiple related phenotypes in COPD, the overlap in exclusively clinical COPD traits has not been investigated. In addition, genome-wide association studies^{31–32} and subsequent meta-analyses have identified genetic loci associated with COPD phenotypes, but most have not been assessed in gene expression studies.³³ By examining several clinical phenotypes across multiple COPD domains, we were able to compare gene sets and over-represented pathways within and across the phenotypes and case-control status. We were unable to recapitulate the genes associated with COPD in genome-wide association studies^{34–35} in the overlap of genes differentially expressed between the phenotype categories and case-control status.

An important pathway involved in the pathogenesis of COPD is dysregulated immune responses to smoking-induced lung injury.³⁶ In particular, adaptive immune responses to foreign antigens, including those of bacterial, viral and fungal origin, have been implicated in the development of COPD.³⁷ We found that the host-virus interaction pathway was represented in the BMI-Hgb overlap differential gene expression set as well as the PFT-systemic category overlap, which suggests that rather than a generalised disease-wide effect, adaptive immune responses to viruses may play a role in subsets of COPD with worse lung function and systemic disease.

Previous studies have employed transcriptomic techniques, including RNA-seq, to identify genes and pathways relevant to COPD diagnosis or related phenotypes, including cigarette smoking,⁸ FEV₁

and imaging characteristics. Bhattacharya and colleagues used RNA microarray analysis from lung tissue obtained during surgical resection of lung nodules to identify overlap in differentially expressed genes between FEV₁, FEV₁:FVC ratio, and case-control status.³⁸ The authors found fewer differentially expressed genes associated with FEV₁ and case-control status, but found genes substantially more associated with FEV₁:FVC. In addition, in the Gene Ontology analysis, the authors found pathways primarily associated with transcription, but also found pathways related to cell components, including the nucleoplasm. Our group has also previously used microarray gene expression profiling on resected lung tissue from subjects with severe COPD and developed gene modules associated with FEV₁ and FEV₁:FVC ratio. The enriched pathways included multiple cellular process and immune system pathways.³⁹ We similarly found a predominance of cell component and process pathways, such as autophagy, represented in the overlap of genes differentially expressed among the three phenotypical categories, including PFTs. Autophagy has been previously implicated as a central process to the dysregulated immune response found in chronic lung diseases, including COPD.⁴⁰ We previously used RNA-seq to compare differential gene expression in multiple phenotypes in bronchial epithelium, alveolar macrophages and peripheral blood from COPD subjects.³ We did not identify specific differentially expressed genes across the three tissues for any phenotype, but did find immune signalling pathways overlapped between all tissues in the associations with emphysema. The current study included a sample size an order of magnitude larger than any previous COPD gene expression study. While most pathways involved cell processes and cell components, we found a

Table 3 Biological pathways enriched in three domain (PFT–systemic–symptom) overlap and the largest phenotype overlap, BMI–Hgb

Phenotype	Database	Pathway	Genes (n)	Bonferroni-corrected P value
PFT–systemic–symptom overlap	UniProt	Phosphoprotein	70	<0.0001
	UniProt	Polymorphism	81	0.022
	Gene Ontology	Cytosol	35	0.027
BMI–Hgb overlap	UniProt	Phosphoprotein	554	<0.0001
	UniProt	Acetylation	289	<0.0001
	Gene Ontology	Cytosol	276	<0.0001
	UniProt	Cytoplasm	325	<0.0001
	Gene Ontology	Protein binding	554	<0.0001
	UniProt	Ubiquitin-like conjugation	140	<0.0001
	Gene Ontology	Cytoplasm	350	<0.0001
	Gene Ontology	Extracellular exosome	212	<0.0001
	UniProt	Mutagenesis site	166	<0.0001
	Gene Ontology	Membrane	170	<0.0001
	UniProt	Ubiquitin-like conjugation pathway	67	<0.0001
	Biocarta	Hgb's chaperone	10	<0.0001
	Gene Ontology	Nucleus	345	<0.0001
	UniProt	Hereditary haemolytic anaemia	12	<0.0001
	UniProt	Blood group antigen	11	0.00052
	Gene Ontology	Proteasome-mediated ubiquitin-dependent protein catabolism	31	0.00093
	UniProt	Autophagy	21	0.0011
	Gene Ontology	Erythrocyte differentiation	13	0.0019
	UniProt	Apoptosis	50	0.0026
	UniProt	Methylation	79	0.0027
	UniProt	Isopeptide bond	86	0.0044
	KEGG	Legionellosis	14	0.0045
	Gene Ontology	Ubiquitin protein ligase binding	35	0.005
	Gene Ontology	Hgb complex	7	0.0063
	UniProt	Haeme biosynthesis	7	0.0097
	UniProt	Leber hereditary optic neuropathy	6	0.02
	UniProt	Proto-oncogene	27	0.02
	UniProt	Mitochondrion	82	0.025
	Gene Ontology	Mitophagy	11	0.027
	Gene Ontology	Nucleoplasm	183	0.037
	Gene Ontology	Cortical cytoskeleton	8	0.38
	UniProt	Host–virus interaction	36	0.05

Data presented as phenotype overlap category, pathway library, pathway, number of genes and Bonferroni corrected p value.
 BMI, Body Mass Index; Hgb, haemoglobin; PFT, pulmonary function test.

small but novel set of differentially expressed genes that exhibited a consistent pattern among all phenotypes.

Several of the clinical COPD phenotypes are statistically correlated and often used interchangeably in the clinical setting; however, the molecular basis for their relatedness and complementarity remains unclear. Previous studies have shown the correlation between the clinical traits.^{41 42} However, there are no previous studies correlating genes and pathways associated with the clinical phenotypes. Our study revealed similar correlation patterns between the PFT and symptom domains but a different pattern in the systemic domain. These findings offer mechanistic support to the complementary use of symptom measures and PFTs in multidimensional grading systems. On the other hand, these findings suggest that the systemic components may not have the same interchangeability as the other domains.

There were several limitations to our study. First, cell and tissue types are known to affect gene expression and using whole-blood

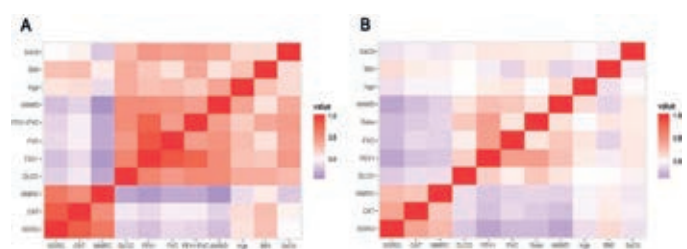


Figure 2 Heatmaps of clinical outcome correlations (A) and gene expression correlations (B). The row and column labels indicate the phenotype variable. The phenotypes are arranged by domain. The Spearman correlation was calculated for each pair of results and plotted in the heatmap. 6MWD, 6 min walk distance; CAT, COPD Assessment Test; DLCO, diffusion capacity of carbon monoxide; Hgb, haemoglobin; MMRC, Modified Medical Research Council; SaO₂, arterial oxygen saturation; SGRQ, St. George's Respiratory Questionnaire.

Table 4 Phase III subject characteristics

Characteristics	Mean (SD) or n (%)
N	960
Age (years)	69.07 (8.42)
Male sex	473 (49.3)
Non-Hispanic white	711 (74.1)
African–American	249 (25.9)
Current smoker	301 (32.1)
Smoking pack-years	43.37 (23.61)
GOLD stage	
PRISm	102 (10.6)
Normal spirometry	419 (43.6)
GOLD 1	117 (12.2)
GOLD 2	189 (19.7)
GOLD 3	90 (9.4)
GOLD 4	43 (4.5)
FEV ₁ % predicted, postbronchodilator	79.43 (25.17)

Data presented as mean (SD) or %.
GOLD, Global Initiative for Chronic Obstructive Lung Disease; PRISm, preserved ratio impaired spirometry.

RNA-seq may be more enriched for immune processes rather than other lung tissue-specific mechanisms, including pathways related to injury and repair. However, previous studies have shown pathway level concordance between tissue gene expression³ and replication of gene expression patterns in whole blood between different study cohorts.⁴³ In addition, using whole blood may facilitate capturing systemic effects of COPD in a way that lung tissue may not. Second, we performed RNA-seq on the largest, well-phenotyped cohort of smokers with and without COPD, and while there are currently no comparable cohorts available for replication studies, we were able to longitudinally validate several of our findings. Third, we did not pursue a global statistical test to establish overlap of gene expression sets. Instead, we relied on a series of gene association tests adjusted for false discovery and subsequent pathway associations again conservatively adjusted for multiple testing to support our findings. Finally, our study included non-Hispanic White and African–American subjects. Cluster analyses have demonstrated different clinical clusters with associated biological networks, depending on population ancestry.⁴⁴ Therefore, similar studies in other populations may yield additional insights.

CONCLUSIONS

In a large study of whole-blood RNA-seq in the COPDGene study, we identified unique gene sets and pathways that overlap between 12 COPD-related phenotypes and case–control status. We demonstrated that the overlapping genes were also associated with COPD progression. While we did not identify any pathways represented in the overlap between the three phenotypical domains and case–control status, we identified multiple genes that demonstrate a consistent pattern of change across many of the phenotypes and case–control status. Several pathways were found to overlap between many of the COPD-related traits, including those involved in adaptive immunity and viral response. Patterns of gene expression correlation were generally similar to the correlation of the clinical phenotypes, except for the systemic phenotypes, which showed negative intradomain correlation and negative correlation with the symptom domain. Further studies will be needed to replicate the predictive capability of the transcriptional signature and to identify causal pathways involved in the pathogenesis of the various features of COPD.

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REFERENCES

- Global initiative for chronic obstructive lung disease: gold report 2019 2019:1–155.
- Kim S, Oh J, Kim Y-I, et al. Differences in classification of COPD group using COPD assessment test (cat) or modified medical Research Council (mMRC) dyspnea scores: a cross-sectional analyses. *BMC Pulm Med* 2013;13:35.
- Morrow JD, Chase RP, Parker MM, et al. RNA-Sequencing across three matched tissues reveals shared and tissue-specific gene expression and pathway signatures of COPD. *Respir Res* 2019;20:1–12.
- Yun JH, Chase R, Parker MM, et al. Peripheral blood gene expression signatures of eosinophilic chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2019;61:398–401.
- Safarali A, Yun JH, Lee S, et al. Transcriptomic signature of Asthma-Chronic obstructive pulmonary disease overlap in whole blood. *Am J Respir Cell Mol Biol* 2021;64:268–71.
- Bouez A, Pham B, Chase R, et al. Integrative genomics analysis identifies ACVR1B as a candidate causal gene of emphysema distribution. *Am J Respir Cell Mol Biol* 2019;60:388–98.
- Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2011;7:32–43.
- Parker MM, Chase RP, Lamb A, et al. RNA sequencing identifies novel non-coding RNA and exon-specific effects associated with cigarette smoking. *BMC Med Genomics* 2017;10:1–10.
- Regan EA, Lynch DA, Curran-Everett D, et al. Clinical and radiologic disease in smokers with normal spirometry. *JAMA Intern Med* 2015;175:1539–49.
- Kim V, Crapo J, Zhao H, et al. Comparison between an alternative and the classic definition of chronic bronchitis in COPDGene. *Ann Am Thorac Soc* 2015;12:332–9.
- Maselli DJ, Bhatt SP, Anzueto A, et al. Clinical epidemiology of COPD: insights from 10 years of the COPDGene study. *Chest* 2019;156:228–38.
- Ritchie ME, Phipson B, Wu D, et al. limma powers differential expression analyses for RNA-seq and microarray studies. *Nucleic Acids Res* 2015;43:e47.
- Vitnuda A, Brown AA, Buil A, et al. Age-Dependent changes in mean and variance of gene expression across tissues in a twin cohort. *Hum Mol Genet* 2018;27:732–41.
- Huan T, Johannes R, Schurmann C, et al. A whole-blood transcriptome meta-analysis identifies gene expression signatures of cigarette smoking. *Hum Mol Genet* 2016;25:ddv288–23.
- Leek JT, Johnson WE, Parker HS, et al. The SVA package for removing batch effects and other unwanted variation in high-throughput experiments. *Bioinformatics* 2012;28:882–3.
- Chen H, Boutros PC. VennDiagram: a package for the generation of highly-customizable Venn and Euler diagrams in R. *BMC Bioinformatics* 2011;12:35.
- Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene Lists using David bioinformatics resources. *Nat Protoc* 2009;4:44–57.
- Wickham H. ggplot2: elegant graphics for data analysis. 2019. Available: <https://cran.r-project.org/web/packages/ggplot2/index.html>
- Deng HK, Unutmaz D, KewalRamani VN, et al. Expression cloning of new receptors used by simian and human immunodeficiency viruses. *Nature* 1997;388:296–300.
- Kim SW, Xiang W, Kovac C, et al. GPR15-mediated homing controls immune homeostasis in the large intestine mucosa. *Science* 2013;340:1456–9.
- Lahl K, Sweere J, Pan J, et al. Orphan chemotactic receptor GPR15 mediates dendritic epidermal T-cell recruitment to the skin. *Eur J Immunol* 2014;44:2577–81.
- Bauer M, Fink B, Seyfarth H-J, et al. Tobacco-Smoking induced GPR15-expressing T cells in blood do not indicate pulmonary damage. *BMC Pulm Med* 2017;17:1–9.
- Budanov AV, Lee JH, Karin M. Stressin' Sestrins take an aging fight. *EMBO Mol Med* 2010;2:388–400.
- Sternier-Kock A, Thorin IS, Koli K, et al. Disruption of the gene encoding the latent transforming growth factor-beta binding protein 4 (LTBP4) causes abnormal lung development, cardiomyopathy, and colorectal cancer. *Genes Dev* 2002;16:2264–73.
- Wempe F, De Zolt S, Koli K, et al. Inactivation of sestrin 2 induces TGF-beta signaling and partially rescues pulmonary emphysema in a mouse model of COPD. *Dis Model Mech* 2010;3:246–53.
- Honkala AT, Tailor D, Malhotra SV. Guanylate-Binding protein 1: an emerging target in inflammation and cancer. *Front Immunol* 2019;10:1–10.
- Liu W, Zhao W-J, Wu Y-H. Study on the differentially expressed genes and signaling pathways in dermatomyositis using integrated bioinformatics method. *Medicine* 2020;99:e21863.
- Wang Z, Zheng T, Zhu Z, et al. Interferon gamma induction of pulmonary emphysema in the adult murine lung. *J Exp Med* 2000;192:1587–600.
- Chen J, Liu A, Lin Z, et al. Downregulation of the circadian rhythm regulator HLF promotes multiple-organ distant metastases in non-small cell lung cancer through PPAR-NF-κB signaling. *Cancer Lett* 2020;482:56–71.
- Harten SK, Oey H, Bourke LM, et al. The recently identified motif of murine metastable epialleles, rearranged L-myc fusion, is involved in maintaining epigenetic marks at CpG island shores and enhancers. *BMC Biol* 2015;13:1–15.
- Kong X, Cho MH, Anderson W, et al. Genome-Wide association study identifies BICD1 as a susceptibility gene for emphysema. *Am J Respir Crit Care Med* 2011;183:43–9.
- McDonald M-LN, Cho MH, Sorheim I-C, et al. Common genetic variants associated with resting oxygenation in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2014;51:678–87.
- Silverman EK, Loscalzo J. Network medicine approaches to the genetics of complex diseases. *Discov Med* 2012;14:143–52.
- Hobbs BD, Hersh CP. Integrative genomics of chronic obstructive pulmonary disease. *Biochem Biophys Res Commun* 2014;452:276–86.
- Sakonsakolpat P, Prokopenko D, Lamontagne M, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. *Nat Genet* 2019;51:494–505.
- Agusti A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med* 2019;381:1248–56.
- Hogg JC, Chu F, Uokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–53.
- Bhattacharya S, Srisuma S, Demeo DL, et al. Molecular biomarkers for quantitative and discrete COPD phenotypes. *Am J Respir Cell Mol Biol* 2009;40:359–67.
- Morrow JD, Zhou X, Lao T, et al. Functional interactors of three genome-wide association study genes are differentially expressed in severe chronic obstructive pulmonary disease lung tissue. *Sci Rep* 2017;7:1–11.
- Choi AMK, Rytter SW, Levine B. Mechanisms of disease: autophagy in human health and disease. *N Engl J Med* 2013;368:651–62.
- Jones PW, Adamek L, Nadeau G, et al. Comparisons of health status scores with MRC grades in COPD: implications for the gold 2011 classification. *Eur Respir J* 2013;42:647–54.
- YS J, Park S, Kim DK. The cutoff point of clinical chronic obstructive pulmonary disease questionnaire for more symptomatic patients. *BMC Pulm Med* 2018;18:1–7.
- Chang Y, Glass K, Liu Y, et al. Copd subtypes identified by network-based clustering of blood gene expression. *Genomics* 2016;107:51–6.
- Thew PY, Ko FWS, Narayana JK, et al. "High-Risk" clinical and inflammatory clusters in COPD of Chinese descent. *Chest* 2020;158:145–56.





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

1 vez dia¹

Zimbus® breezhaler®

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

NOVA
ASSOCIAÇÃO
LABA/LAMA
/ICS¹

Dá ritmo à vida^{2,3*}

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

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

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

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

ARTIGO ORIGINAL

Intervenção de alteração comportamental durante seis semanas para reduzir o comportamento sedentário em pessoas com doença pulmonar obstrutiva crônica: um ensaio aleatorizado controlado

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RESUMO

Introdução Este estudo visou determinar se uma intervenção de alteração comportamental durante 6 semanas seria mais eficaz do que uma intervenção falsa para reduzir o comportamento sedentário (CS) em pessoas com doença pulmonar obstrutiva crônica (DPOC).

Métodos Foram recrutadas pessoas com DPOC estável na lista de espera para entrada em reabilitação pulmonar para este ensaio multicêntrico com aleatorização (atribuição independente e oculta) para um grupo de intervenção ou para um grupo falso, com ocultação do avaliador e análise da intenção de tratamento (ITT). A intervenção de alteração comportamental consistiu em sessões semanais com um fisioterapeuta durante 6 semanas para reduzir o CS através da educação, do estabelecimento de objetivos orientados e de *feedback* em tempo real sobre o CS. A intervenção falsa consistiu em chamadas telefônicas semanais durante 6 semanas para monitorizar o estado de saúde. O CS foi medido continuamente durante 7 dias por acelerometria usada nas coxas (activPAL3 micro). O resultado principal foi o tempo despendido em CS. Os participantes com pelo menos 4 dias de ≥ 10 horas de tempo acordado foram incluídos na análise ITT e aqueles que relataram ter alcançado $\geq 70\%$ dos objetivos de redução do CS ou que completaram todas as chamadas falsas foram incluídos numa análise por protocolo.

Resultados Foram recrutados 70 participantes e 65 completaram o estudo (média $\pm$ DP idade 74 $\pm$ 9 anos, FEV₁ média 55% $\pm$ 19% do previsto, 49% masculino). Às 6 semanas, não foram observadas diferenças entre grupos no tempo despendido em CS na análise ITT (diferença média 5 min/dia, 95% IC -38 a 48) ou na análise por protocolo (-16 min/dia, 95% IC -80 a 48).

Discussão Uma intervenção de alteração comportamental durante 6 semanas não reduziu o tempo em CS comparativamente a uma intervenção falsa em pessoas com DPOC estável moderada a grave antes de reabilitação pulmonar.

INTRODUCTION

In people with chronic obstructive pulmonary disease (COPD), it is well established that low levels of physical activity (PA) are associated with an increased risk of mortality and hospitalisation due to acute exacerbations.^{1,2} Interventions to increase PA in people with COPD have been investigated extensively over the last decade,^{3–5} but much less is known about interventions to reduce sedentary behaviour (SB) in this population.⁶

SB is defined as 'any waking behaviour characterised by an energy expenditure ≤ 1.5 metabolic equivalents, while in a sitting, reclining or lying posture',⁷ and is a distinct construct from physical inactivity, which refers to insufficient levels of PA to meet current recommendations.⁸ The importance of reducing SB in people with COPD is based on several factors. First, people with COPD spend more time in SB compared with healthy age-matched peers.^{9–12} Second, consistent associations

Key messages

What is the key question?

► Can a 6-week behaviour change intervention reduce sedentary behaviour in people with chronic obstructive pulmonary disease (COPD)?

What is the bottom line?

► A 6-week behaviour change intervention did not reduce time spent in sedentary behaviour in people with stable moderate-to-severe COPD but may have positive effects on physical activity.

Why read on?

► The results of this study will inform the participant selection, design and timing of future interventions that aim to reduce sedentary behaviour and increase physical activity in people with COPD.

of SB with mortality risk^{13–14} and cardiometabolic disease^{15–16} have been observed in small longitudinal studies of COPD. Lastly, reducing SB may be a more feasible strategy for improving health outcomes in people with COPD than targeting moderate-to-vigorous-intensity PA (MVPA) alone.¹⁷ Preliminary evidence suggests that behaviour change interventions, defined as 'coordinated sets of activities designed to change specified behaviour patterns',¹⁸ may be effective and feasible for reducing SB in older adults.^{19–20} Such interventions are underpinned by theoretical models of behavioural change and often include education, goal setting, self-monitoring of and feedback on behaviour to facilitate change.²¹

To date, only one pilot study (COPD-sitting and exacerbations trial (SEAT)) has examined the feasibility and acceptability of a behaviour change intervention to reduce SB in people with COPD.²² This intervention was delivered on discharge from hospital following an acute exacerbation and consisted of a single education session and provision of a wearable activity tracker to self-monitor SB for 2 weeks. Although the intervention components were viewed positively by participants, uptake and retention of the intervention were low and being unwell and overwhelmed after an exacerbation were reported as the main reasons for not engaging with the intervention.²² These findings suggest that behaviour change interventions targeting SB may need to be of a longer duration with more frequent contact with a healthcare professional and conducted in people with COPD who are clinically stable.



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The primary aim of this study was to determine, in people with stable COPD, whether a 6-week behaviour intervention was more effective than a sham intervention in reducing time spent in SB. The secondary aims of the study were to determine: (1) the effects of the behaviour change intervention on patterns of SB accumulation, PA, functional exercise capacity, health-related quality of life (HRQoL), patient activation, anxiety, depression and attendance and completion of pulmonary rehabilitation and (2) the feasibility of the behaviour change intervention with respect to uptake, retention and compliance.

METHODS

Study design and participants

This study was a prospective multicentre randomised controlled trial with concealed allocation and assessor blinding, comparing a 6-week behaviour change intervention with a sham intervention to reduce SB. The study was registered with the Australian New Zealand Clinical Trials Registry (identifier ANZCTR12616001534471) and complies with the Consolidated Standards of Reporting Trials Statement for the reporting of randomised controlled trials.²³ The full protocol has been published previously.²⁴ In brief, participants with a confirmed diagnosis of COPD on spirometry²⁵ and who were clinically stable were recruited from the waitlist for pulmonary rehabilitation at five participating sites, and randomised into an intervention group or sham group with stratification for 6 min walk distance (6MWD) (<350 vs ≥350 m) and prior attendance at pulmonary rehabilitation. Informed written consent was obtained from all participants.

The behaviour change intervention

The behaviour change intervention has been reported according to the Template for Intervention Description and Replication²⁶ and consisted of six once weekly sessions with a physiotherapist to reduce SB via three target behaviours: replace SB with stepping, replace SB with standing and break up prolonged bouts of SB. The intervention was informed by the 'capability, opportunity, motivation, behaviour' (COM-B) model²⁷ and used the Behaviour Change Wheel to systematically select appropriate behavioural change techniques from the Behaviour Change Technique Taxonomy (v1) to reduce SB.²⁸ To ensure fidelity, the principal investigator assessed their delivery of the intervention against a checklist of content and documented if any components of the intervention were not delivered. Application of the COM-B model to our current understanding of high levels of SB in people with COPD,¹⁷ with practical examples of how behavioural change techniques were linked to the Behaviour Change Wheel¹⁸ and were implemented during the intervention, is illustrated in online supplemental table 1.

The sham intervention

The sham intervention consisted of six once weekly phone calls to monitor health status. Full details regarding the content and delivery of the behavioural change and sham interventions have been described previously²⁴ and can be found in online supplemental data.

Outcome measures

The primary outcome was time spent in SB expressed in min/day. Time in SB was measured using thigh-worn accelerometry (activPAL3 micro; PAL Technologies, Glasgow, Scotland, UK) continuously over 7 days. The minimum wear time for inclusion of SB data was set at 4 days for at least ten hours per day.²⁹ Participants were classified as having 'high' SB levels at baseline if SB accounted for >70% of waking wear time.^{13 30} The minimal detectable change (MDC) reflects the minimal change in outcome score that corresponds to a real change in SB for an individual, with the most sensitive measures having the lowest MDC.³¹ The MDC for time spent in SB has not yet been determined in COPD but was reported as -2.7% of waking wear time in older adults.³² Full details on SB data collection and processing have been described previously.³⁰

Secondary outcomes were patterns of SB accumulation and PA measured using the activPAL3 micro and calculated based

on waking wear time (ie, sleep and periods of non-wear were removed from the analysis); functional exercise capacity using the 6 min walk test (6MWT)³³; HRQoL using the St George's Respiratory Questionnaire (SGRQ)³⁴; patient activation using the Patient Activation Measure (PAM)³⁵; anxiety and depression using the Hospital Anxiety and Depression Scale³⁶; attendance and completion of pulmonary rehabilitation; and feasibility of the behaviour change intervention. All outcome measures were taken at baseline (ie, prior to randomisation) and at end-intervention (ie, at completion of the 6-week intervention period prior to pulmonary rehabilitation).

Although there is no universally accepted measure of SB accumulation, prolonged SB (ie, SB accumulated in unbroken bouts of ≥30 min) and usual bout duration have commonly been used in large population-based studies^{37–41} and have demonstrated sensitivity to change following interventions in office workers and older adults.³² Usual bout duration is defined as the duration of the sedentary bout corresponding to 50% of daily accumulated sedentary time and is most often calculated using non-linear regression, where higher values indicate the accumulation of SB in fewer, prolonged bouts.^{32 42} In the occupational setting, an MDC of -6.44 min has been reported for usual bout duration.^{43 44} The minimal important difference (MID) in PA has been reported as 600–1100 steps/day in people with COPD following pulmonary rehabilitation.⁴⁵ Definitions of the SB and PA outcomes are provided in online supplemental table 2.

Three measures were used to assess feasibility of the behaviour change intervention: uptake (proportion of eligible participants who enrolled in the study); retention (proportion of enrolled participants assessed at 6 weeks); and compliance with the intervention (participants' self-reported achievement of their main goal to reduce SB). Of a maximum 21 goals that could be set during the 6-week intervention period (ie, cumulative sum of setting one goal in the first week, followed by two goals in the second week, etc), the number of goals relating to each target behaviour (replace SB with stepping, replace SB with standing and break up prolonged bouts of SB) was calculated for each participant. The target behaviour that represented the highest number of goals set during the intervention period was regarded as the participant's main goal.

Sample size calculation

It was estimated that 70 participants were needed to ensure that 64 participants completed the study, allowing for a 10% lost to follow-up.⁴⁶ This sample size was sufficient to provide 80% power to detect as significant, at the (two sided) 5% level, a minimum 75 min/day difference in total SB between the intervention and sham groups using a two-sample t-test, assuming an SD of 108 min/day in total SB.⁴⁷

Data analysis

Data were analysed using SPSS V.25 (IBM) on an intention-to-treat basis. Within-group comparisons were analysed using paired t-tests. Between-group comparisons were analysed using analysis of covariance with baseline values for each respective outcome entered into the model as a continuous covariate. Compliance rates with home-based pulmonary rehabilitation, which have been approximated at 70%,^{48 49} were used to inform the minimum goal achievement indicating compliance with the behaviour change intervention. Participants in the intervention group who reported achieving ≥70% of their main goal and participants in the sham group who completed all six sham calls were regarded as compliant with the intervention and were included in a per-protocol analysis using the same methods as the primary analysis.

RESULTS

Participant flow and characteristics

Seventy participants were recruited from December 2016 to April 2019, with 34 randomised to the intervention group and 36 to the sham group, of which 65 participants completed the study and 64 participants contributed SB data to the primary analysis. This represented an uptake of 32% and retention of 93% (figure 1). Primary reasons for declining to participate in the trial were lack of interest due to a perception of already having low SB levels and being unable to commit due to medical or social issues. Reasons for withdrawal from the study were moving

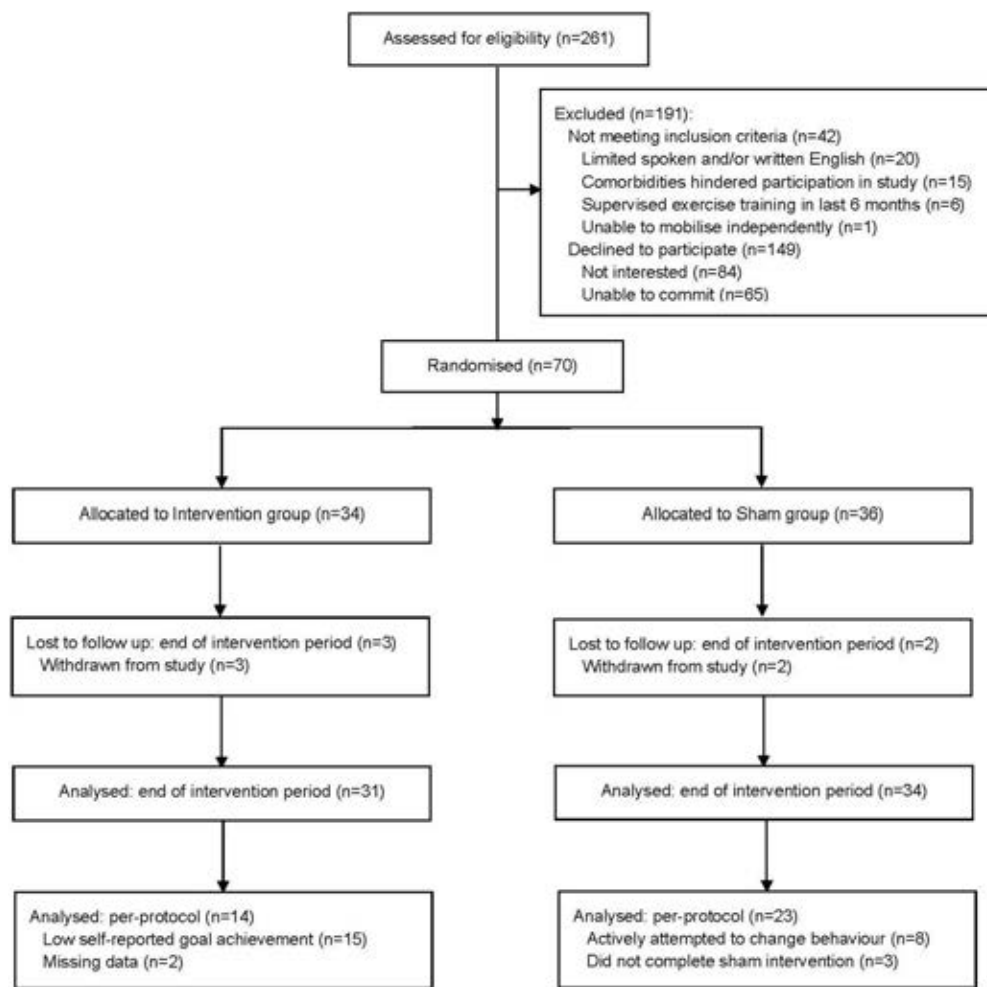


Figure 1 Flow of participants.

outside metropolitan Sydney (n=1), worsening of sciatic pain requiring corticosteroid injection (n=1) and perceived lack of benefit (n=3). The intervention and sham groups were similar for lung function, 6MWD and prevalence of comorbidities at baseline (table 1).

Engagement and compliance with the intervention

Twenty-two participants (73%) chose to replace SB with stepping as their main goal, which commonly involved walking for leisure or transport. Five participants (17%) chose to replace SB with standing as their main goal, commonly by standing up to perform domestic tasks. Three participants (10%) chose to break up prolonged SB as their main goal, commonly by moving after 30 min of uninterrupted screen time, reading or crafts. On average, the main goal accounted for 64% (SD 16) of all goals set during the intervention. Twenty participants (65%) were successful in setting six goals to reduce SB. Mean self-reported goal achievement was 64% (SD 28). Nineteen participants (61%) reported consistent use of the wearable activity tracker over the 6 weeks.

Sixteen participants (52%) in the intervention group and 11 participants (32%) in the sham group reported a worsening of their health status during the intervention period (worsening of COPD symptoms or a new onset of and/or worsening of existing musculoskeletal pain). Fourteen participants (48%) were regarded as compliant with the behaviour change intervention and 31 participants (91%) in the sham group as compliant with the sham intervention.

Intention-to-treat analyses

Time in SB

The baseline and end-intervention values for time spent in SB are shown in table 2. There was no between-group difference in time spent in SB. Non-significant within-group reductions in SB were observed for both the intervention and sham groups.

Secondary outcomes

The baseline and end-intervention values for SB accumulation and PA are shown in table 2 and online supplemental table 3. There were no significant differences in SB accumulation or PA between groups. In the intervention group, within-group analyses showed no significant changes in SB accumulation but significant increases in step count and MVPA. The baseline and end-intervention values for functional exercise capacity, HRQoL, patient activation, anxiety and depression are shown in online supplemental table 3. Significant between-group differences favouring the intervention group were observed for SGRQ-Activity score and PAM score.

Twenty-seven participants (79%) in the intervention group and 31 participants (86%) in the sham group attended pulmonary rehabilitation following the 6-week intervention. Completion rates of pulmonary rehabilitation were 50% in the intervention group and 56% in the sham group, with no significant differences in attendance or completion of pulmonary rehabilitation between groups.

Per-protocol analyses

Fourteen of 31 participants in the intervention group and 31 of 34 participants in the sham group were included in the per-protocol analyses. The baseline and end-intervention values for time spent in SB are shown in table 3. Per-protocol analyses for SB accumulation and PA are shown in table 3 and online supplemental table 4, and for functional exercise capacity, HRQoL, patient activation, anxiety and depression in online supplemental table 4.

Time in SB

Similar to the intention-to-treat analyses, no between-group difference in time in SB was observed and there were non-significant within-group reductions in SB in both groups.

Secondary outcomes

Similar to the intention-to-treat analyses, no significant between-group differences or within-group differences in the intervention group were observed for any SB accumulation measures. However, significant between-group differences favouring the intervention group were observed for MVPA and step count, which exceeded the upper end of the MID of 1100 steps/day (2037 steps/day, 95% CI 871 to 3204), and for HAD depression score.

Table 1 Participant characteristics

Characteristic	Participants		
	Intervention (n=31)	Sham (n=34)	Lost to follow-up (n=5)
Age, years	74 (9)	73 (10)	70 (8)
Sex, n males (%)	16 (52)	16 (47)	2 (40)
Employment status, n (%)			
Retired	22 (71)	30 (88)	5 (100)
Part time	6 (19)	4 (12)	0
Full time	3 (10)	0	0
Lung function			
FEV ₁ , L	1.43 (0.60)	1.34 (0.50)	1.63 (0.57)
FVC, L	2.62 (0.77)	2.66 (0.77)	3.00 (0.75)
FEV ₁ % predicted	58 (20)	53 (19)	61 (18)
GOLD grade, n (%)			
1	4 (13)	3 (9)	1 (20)
2	15 (48)	10 (29)	3 (60)
3	10 (32)	20 (59)	1 (20)
4	2 (7)	1 (3)	0
BMI, kg/m ² †	28.5 (7.1)	27.5 (6.4)	31.4 (15.7)
Smoking status, n (%)			
Former	27 (87)	29 (85)	5 (100)
Current	4 (13)	5 (15)	0
Smoking history, pack-years	41 (28)	42 (23)	49 (11)
≥1 self-reported COPD hospital admission in last 6 months, n (%)	23 (74)	23 (68)	3 (60)
Comorbidities, n (%)			
Cardiometabolic	26 (84)	26 (77)	4 (80)
Other respiratory	16 (52)	13 (38)	2 (40)
Musculoskeletal	20 (65)	26 (77)	4 (80)
Mental health	6 (19)	13 (38)	1 (20)
6MWD, m	366 (106)	353 (95)	332 (117)
6MWD % predicted	62 (16)	59 (14)	58 (16)
Mobilises with walking aid, n (%)	3 (10)	7 (21)	1 (20)
Exercise-induced oxygen desaturation‡, n (%)	13 (42)	16 (50)	3 (60)
Previous pulmonary rehabilitation†, n (%)	8 (26)	9 (27)	2 (40)

Values are presented as mean (SD) unless otherwise stated.

*P<0.05 was considered significant.

†Self-reported attendance to a pulmonary rehabilitation programme. Participants who undertook formal exercise training in the last 6 months were excluded from the study.

‡Defined as desaturation to <90% during a 6 min walk test. Two participants in the sham group received long-term oxygen therapy and were excluded from the count. BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 6MWD, 6 min walk distance.

DISCUSSION

A 6-week behaviour change intervention did not reduce time spent in SB nor the accumulation of SB in prolonged bouts compared with a sham intervention in people with stable COPD. Although not the primary focus of the intervention, per-protocol analyses showed statistically and clinically significant improvements in step count and MVPA favouring the intervention group. There was low uptake of, and moderate compliance with, the behaviour change intervention in this group of participants on the waitlist for pulmonary rehabilitation, which suggests that it may not be feasible to target SB in all people with COPD prior to engagement in a comprehensive pulmonary rehabilitation programme.

This is the first study to evaluate the effects of a pragmatic behaviour change intervention to reduce SB in COPD using a randomised parallel-group study design with intention-to-treat analysis and thigh-worn accelerometry to characterise SB. The intervention was informed by behavioural change theory, used standardised frameworks to analyse behaviour and systematically select appropriate behavioural change techniques, and was delivered by the same principal investigator against a checklist of content to ensure fidelity. The behaviour change intervention, however, had no effect on time in SB or the accumulation of SB in prolonged bouts when compared with the sham intervention. Randomised controlled trials conducted in older adults with coronary artery disease and stroke have also failed to show significant reductions in SB following behaviour change interventions of 6–7 weeks' duration, despite evidence that the interventions were safe, feasible and viewed positively by participants.^{19–46} Thus far, the effectiveness of behaviour change interventions for reducing SB in older adults has only been observed in small non-randomised studies.^{20–50–51} The lack of effect on SB across different clinical populations suggests that further exploration of intervention content, delivery, timing, and participant selection is necessary in order to determine the optimal dose of intervention required to reduce SB in people with pre-existing disease.

We propose several hypotheses for the lack of difference in SB between the intervention and sham groups: (1) a 6-week intervention period was chosen to align with waiting times for entry into pulmonary rehabilitation but may have been of an insufficient duration for new habit formation, which is typically expected to take ten weeks of daily repetition⁵²; (2) compliance with the behaviour change intervention was 64%, and subsequently the intervention may have been of an insufficient dose to elicit change; and (3) unexpected large and favourable within-group changes in SB were observed in the sham group.

Approximately two-thirds of the intervention group were able to set six goals to reduce SB and reported achieving these goals each week. The most frequently reported reason for not setting additional goals and non-achievement of goals was feeling unwell, followed by other medical or social issues taking priority over participation in the study, and then by perceived lack of need for change. Over half the participants in the intervention group reported worsening of COPD symptoms and/or complaints of musculoskeletal pain during the intervention, which impaired their physical capacity to reduce SB. Given the initial hypothesis that reducing SB would be a physiologically realistic interim step to exercise training and higher intensity PA, it was surprising that such a high proportion of participants attributed lack of compliance with the intervention to physical limitations. People with COPD who report disease-specific limitations as the main barrier to reducing SB may first need to undergo pulmonary rehabilitation to improve their symptoms and exercise capacity before it is feasible to engage in a behaviour change intervention targeting SB.

Only 61% of participants in the intervention group reported consistent engagement with the activity tracker, which is low compared with published PA telecoaching studies in COPD^{53–55} and requires further investigation using qualitative designs. While activity trackers have been used previously to self-monitor and provide feedback on step count, the main purpose of the activity tracker in this study was to prompt breaks in SB every 30 min.

Table 2 Within-group and between-group intention-to-treat analyses for SB and physical activity

Outcome measure	Intervention group			Sham group			Adjusted between-group difference	
	Baseline (n=30)	End intervention (n=30)	Within-group difference (n=30)	Baseline (n=34)	End intervention (n=34)	Within-group difference (n=34)	Intervention minus Sham (n=64)	P value
Total SB								
Waking wear time, min/day	909 (85)	907 (86)	-2 (-22 to 19)	908 (68)	901 (60)	-7 (-24 to 11)	5 (-20 to 30)	0.67
Time spent in SB, min/day	643 (108)	624 (106)	-19 (-58 to 20)	642 (109)	618 (124)	-24 (-51 to 3)	5 (-38 to 48)	0.81
Time spent in SB as % waking wear time, %	70.7 (9.8)	68.8 (10.7)	-1.9 (-5.8 to 2.0)	70.9 (11.6)	68.5 (12.6)	-2.3 (-4.9 to 0.2)	0.4 (-3.9 to 4.7)	0.84
Patterns of SB accumulation								
Prolonged SB†, min/day	380 (149)	341 (128)	-39 (-83 to 4)	370 (145)	336 (153)	-34 (-65 to -3)*	-2 (-50 to 46)	0.93
Prolonged SB as % waking wear time, %	41.5 (15.0)	37.5 (13.4)	-4.0 (-8.6 to 0.5)	40.9 (16.0)	37.2 (16.6)	-3.7 (-7.1 to -0.2)*	-0.2 (-5.3 to 4.9)	0.94
Usual bout duration‡, min	39.6 (22.0)	33.9 (15.0)	-5.6 (-12.9 to 1.6)	38.4 (18.0)	34.5 (15.4)	-3.9 (-7.1 to -0.7)*	-1.2 (-6.9 to 4.5)	0.68
Physical activity								
Step count, steps/day	4945 (2576)	5939 (3541)	994 (115 to 1873)*	4636 (2667)	4862 (2643)	226 (-139 to 591)	779 (-121 to 1679)	0.09
Time spent in light activities§, min/day	228 (76)	237 (86)	9 (-22 to 40)	229 (97)	245 (105)	16 (-5 to 37)	-7 (-42 to 28)	0.67
Time spent in light activities as % waking wear time¶, %	25.1 (8.4)	26.0 (9.3)	0.9 (-2.7 to 4.6)	25.2 (10.5)	27.3 (11.7)	2.1 (-0.3 to 4.5)	-1.2 (-5.2 to 2.8)	0.55
Time spent in MVPA††, min/day	39 (22)	47 (29)	8 (1 to 16)*	36 (22)	38 (22)	2 (-2 to 5)	7 (-1 to 15)	0.07
Time spent in MVPA as % waking wear time‡‡, %	4.2 (2.3)	5.2 (3.0)	1.0 (0.2 to 1.7)*	3.9 (2.3)	4.1 (2.3)	0.2 (-0.1 to 0.6)	0.7 (-0.1 to 1.5)	0.07

Values are presented as mean (SD) and mean difference (95% CI). Participants with at least four wear days of ≥ 10 hours were included in the ITT analysis.

*P<0.05 was considered significant.

†Time in SB accumulated in bouts of ≥ 30 min.

‡Duration of the sedentary bout corresponding to 50% of daily accumulated time in SB. Higher values indicate a tendency to accumulate SB in more prolonged bouts.

§Time spent standing plus time spent stepping at <3 METs.

¶Proportion of waking wear time spent standing plus time spent stepping at <3 METs.

**Time spent stepping at ≥ 3 METs.

††Proportion of waking wear time spent stepping at ≥ 3 METs.

METs, metabolic equivalents; MVPA, moderate-to-vigorous intensity physical activity; SB, sedentary behaviour.

Participants may have found a single vibrotactile prompt to break up SB difficult to detect or easy to ignore, which may have contributed to lower rates of engagement with the activity tracker and to the lack of intervention effect on SB.

Qualitative studies have suggested that SB is associated with mental health benefits in older adults.⁵⁶ In people with COPD, SB enables rest between activities that cause breathlessness and is perceived as intrinsically enjoyable in the context of a life-limiting, progressive illness.⁵⁷ Qualitative findings from the COPD-SEAT trial indicated that lack of engagement with certain strategies to reduce SB, such as getting up at regular intervals while watching television (TV), was attributed to feelings of intrusion on pleasurable activities and disruption of the enjoyment of life.⁵⁷ Perceptions of lack of benefit may explain why there was limited participant engagement with the 'break up prolonged bouts of SB' strategy to reduce SB and may have contributed to the lack of between-group differences in prolonged SB and usual bout duration. It is a limitation of this study that participants were not involved in the development of the behaviour change

intervention, particularly with respect to interest in reducing SB and timing of the intervention prior to pulmonary rehabilitation. In order to optimise uptake and compliance rates, future interventions targeting SB should be developed in conjunction with people with COPD, their loved ones,¹¹ and health professionals involved in COPD management.

The significant within-group reductions in prolonged SB and usual bout duration in the sham group also warrants further investigation. It is possible that a 'light touch' intervention of attention, combined with the awareness of being monitored and the intrinsic stimulus for change arising from participation in a research study, is sufficient to reduce SB in certain individuals with COPD. The effects of attention on the therapeutic alliance between participants and the principal investigator may have also played a role in facilitating behavioural change in the sham group, but is difficult to capture and report in clinical trials. The relationship between patient and therapist is known to be an important determinant of treatment outcome in psychotherapy, and has been positively associated with treatment adherence and

Table 3 Within-group and between-group per-protocol analyses for SB and physical activity

Outcome measure	High goal achievement in intervention group			Compliant with sham in Sham group			Adjusted between-group difference	
	Baseline (n=14)	End intervention (n=14)	Within-group difference (n=14)	Baseline (n=31)	End intervention (n=31)	Within-group difference (n=31)	Intervention minus Sham (n=45)	P value
Total SB								
Waking wear time, min/day	922 (67)	922 (86)	0 (−34 to 35)	906 (68)	904 (61)	−2 (−21 to 16)	7 (−26 to 40)	0.67
Time spent in SB, min/day	631 (106)	596 (118)	−35 (−118 to 48)	636 (108)	616 (124)	−20 (−49 to 9)	−16 (−80 to 48)	0.61
Time spent in SB as % waking wear time, %	68.3 (10.1)	64.7 (12.0)	−3.6 (−11.9 to 4.5)	70.4 (11.9)	68.1 (12.7)	−2.3 (−5.0 to 0.5)	−2.0 (−8.3 to 4.3)	0.52
Patterns of SB accumulation								
Prolonged SB†, min/day	369 (138)	305 (85)	−64 (−152 to 24)	365 (144)	337 (146)	−28 (−60 to 5)	−35 (−99 to 29)	0.28
Prolonged SB as % waking wear time, %	39.9 (14.5)	33.2 (9.7)	−6.7 (−16.1 to 2.7)	40.4 (16.0)	37.4 (16.6)	−3.0 (−6.6 to 0.5)	−3.8 (−10.8 to 3.1)	0.27
Usual bout duration‡, min	39.0 (26.7)	29.0 (6.6)	−10.0 (−25.9 to 6.0)	38.1 (18.4)	34.6 (15.4)	−3.5 (−6.7 to −0.2)*	−6.0 (−12.9 to 1.0)	0.09
Physical activity								
Step count, steps/day	5971 (2906)	8061 (3642)	2090 (458 to 3721)*	4556 (2556)	4756 (2583)	200 (−147 to 547)	2037 (871 to 3204)	0.001*
Time spent in light activities§, min/day	243 (78)	261 (100)	18 (−49 to 84)	229 (97)	245 (105)	16 (−5 to 37)	3 (−49 to 55)	0.91
Time spent in light activities as % waking wear time¶, %	26.5 (8.9)	28.3 (11.3)	1.8 (−6.1 to 9.7)	25.8 (10.7)	27.9 (11.9)	2.1 (−0.5 to 4.8)	−0.1 (−6.1 to 5.9)	0.98
Time spent in MVPA**, min/day	48 (25)	65 (29)	17 (4 to 31)*	36 (22)	38 (22)	2 (−2 to 5)	18 (8 to 28)	0.001*
Time spent in MVPA as % waking wear time††, %	5.2 (2.6)	7.0 (2.9)	1.8 (0.5 to 3.3)*	3.8 (2.3)	4.0 (2.2)	0.2 (−0.2 to 0.5)	2.0 (0.9 to 3.0)	<0.001*

Values are presented as mean (SD) and mean difference (95% CI). High self-reported goal achievement was defined as $\geq 70\%$ achievement of the main goal. One participant assigned to the intervention group had missing goal achievement data and was excluded from the analysis. Participants in the sham group were regarded as compliant with the sham intervention if they completed all six sham calls.

* $P < 0.05$ was considered significant.

†Time in SB accumulated in bouts of ≥ 30 min.

‡Duration of the sedentary bout corresponding to 50% of daily accumulated time in SB. Higher values indicate a tendency to accumulate SB in more prolonged bouts.

§Time spent standing plus time spent stepping at < 3 METs.

¶Proportion of waking wear time spent standing plus time spent stepping at < 3 METs.

**Time spent stepping at ≥ 3 METs.

††Proportion of waking wear time spent stepping at ≥ 3 METs.

METs, metabolic equivalents; MVPA, moderate-to-vigorous intensity physical activity; SB, sedentary behaviour.

satisfaction, physical function and depressive symptoms in physical rehabilitation settings.⁵⁸

The behaviour change intervention resulted in non-significant increases in step count, which exceeded the lower end of the MID of 600 steps/day,⁴⁵ but did not change time spent standing or in light intensity PA. In the per-protocol analysis, the increase in step count was comparable to that observed following a 12-week semiautomated telecoaching intervention targeting increases in the amount and intensity of PA.⁵⁴ However, given this subgroup analysis was based on a small sample and was not powered to detect changes in SB or PA, these findings should be interpreted with caution. The improvements in PA can be attributed to the large majority of participants who chose to replace SB with stepping as their main goal during the intervention, which is contrary to our previous understanding that increasing standing time and breaking up SB would be more feasible for people with COPD than increasing PA alone.⁵⁹ The preference of most participants to replace SB with stepping may have been influenced by a persisting lack of knowledge about the meaning of SB as distinct from physical inactivity and reinforces the importance of encouraging movement of any intensity in people with COPD. It is also possible that maintaining or increasing SB was perceived as necessary by participants in order to enable greater participation in PA. People with COPD have reported adopting SB as a means to recover from and manage symptoms,⁵⁷ and may explain the clinically relevant increase in step count without concomitant increases in light-intensity PA or reductions in SB. Enhancing overall movement and participation in enjoyable light-intensity PA in people

with COPD, rather than specifically reducing SB, may be more appropriate goals in research and clinical practice.

There are several study limitations. First, people with COPD with 'high' levels of SB, and thus potential to change their behaviour, were not selectively recruited to the study. Low-level evidence suggests that $> 70\%$ of waking wear time spent in SB is linked with increased mortality risk and poorer clinical outcomes in COPD^{13 30} and may be a useful cut-off to indicate 'high' SB in future studies. Second, most participants had moderate or severe airflow obstruction, which may limit the generalisability of the study findings to all people with stable COPD. Third, materials were developed to ensure the behaviour change intervention was administered with fidelity, but fidelity assurance was not formally undertaken. Fourth, SB was assessed using thigh-worn accelerometry at the end of the 6-week intervention period, when participants may have perceived the intervention was complete and were no longer continuing their goals to reduce SB. Fifth, compliance with behaviour change intervention was assessed using participant self-report rather than thigh-worn accelerometry and may have led to over-estimation of compliance with the intervention. In order to accurately determine whether individualised goals to reduce SB during specific activities or contexts are being met (eg, 'Get up and walk around for 2 min during the TV advertisement breaks', 'Stand up to do the ironing instead of sitting down'), future studies should use a combination of self-report and device-based tools to monitor SB during the intervention period. Finally, since the study was not powered to detect between-group changes in SB accumulation or PA, non-significant results should be interpreted with caution.

CONCLUSIONS

A 6-week behaviour change intervention did not reduce time spent in SB compared with a sham intervention in people with stable moderate-to-severe COPD. Further research is needed to determine the optimal intervention design, timing and selection of participants to elicit significant change in SB, before the effects of such interventions on important markers, such as cardiometabolic risk factors, can be evaluated. Reinforcing the concept of 'moving more' and participation in PA of any intensity, rather than 'sitting less', may be a more appropriate focus of behavioural interventions in future studies.

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REFERENCES

- Cheng SWM, McKeough Z, Alison J, et al. Associations of total and type-specific physical activity with mortality in chronic obstructive pulmonary disease: a population-based cohort study. *BMC Public Health* 2018;18:268.
- Gimeno-Santos E, Frei A, Steurer-Stey C, et al. Determinants and outcomes of physical activity in patients with COPD: a systematic review. *Thorax* 2014;69:731–9.
- Burge AT, Cox NS, Abramson MJ, et al. Interventions for promoting physical activity in people with chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2020;4:CD012626.
- Lahham A, McDonald CF, Holland AE. Exercise training alone or with the addition of activity counseling improves physical activity levels in COPD: a systematic review and meta-analysis of randomized controlled trials. *Int J Chron Obstruct Pulmon Dis* 2016;11:3121–36.
- Mantoani LC, Rubio N, McKinsty B, et al. Interventions to modify physical activity in patients with COPD: a systematic review. *Eur Respir J* 2016;48:69–81.
- Hill K, Gardiner PA, Cavalheri V, et al. Physical activity and sedentary behaviour: applying lessons to chronic obstructive pulmonary disease. *Intern Med J* 2015;45:474–82.
- Sedentary Behaviour Research Network. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours". *Appl Physiol Nutr Metab* 2012;37:540–2.
- Tremblay MS, Aubert S, Barnes JD, SBRN Terminology Consensus Project Participants. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. *Int J Behav Nutr Phys Act* 2017;14:75.
- Kawagoshi A, Kiyokawa N, Sugawara K, et al. Quantitative assessment of walking time and postural change in patients with COPD using a new triaxial accelerometer system. *Int J Chron Obstruct Pulmon Dis* 2013;8:397–404.
- McNamara RJ, McKeough ZJ, McKenzie DK, et al. Physical comorbidities affect physical activity in chronic obstructive pulmonary disease: a prospective cohort study. *Respirology* 2014;19:866–72.
- Mesquita R, Nakken N, Janssen DJA, et al. Activity levels and exercise motivation in patients with COPD and their resident Loved ones. *Chest* 2017;151:1028–38.
- Orme MW, Steiner MC, Morgan MD, et al. 24-Hour accelerometry in COPD: exploring physical activity, sedentary behavior, sleep and clinical characteristics. *Int J Chron Obstruct Pulmon Dis* 2019;14:419–30.
- Furlanetto KC, Donária L, Schneider LP, et al. Sedentary behavior is an independent predictor of mortality in subjects with COPD. *Respir Care* 2017;62:579–87.
- Ukawa S, Tamakoshi A, Yatsuya H, et al. Association between average daily television viewing time and chronic obstructive pulmonary disease-related mortality: findings from the Japan collaborative cohort study. *J Epidemiol* 2015;25:431–6.

- McKeough Z, Cheng SWM, Alison J, et al. Low leisure-based sitting time and being physically active were associated with reduced odds of death and diabetes in people with chronic obstructive pulmonary disease: a cohort study. *J Physiother* 2018;64:114–20.
- Park SK, Larson JL. The relationship between physical activity and metabolic syndrome in people with chronic obstructive pulmonary disease. *J Cardiovasc Nurs* 2014;29:499–507.
- Cavalheri V, Straker L, Gucciardi DF, et al. Changing physical activity and sedentary behaviour in people with COPD. *Respirology* 2016;21:419–26.
- Michie S, Atkins L, West R. The behaviour change wheel: a guide to designing interventions. London: Silverback Publishing, 2014.
- English C, Healy GN, Olds T, et al. Reducing sitting time after stroke: a phase II safety and feasibility randomized controlled trial. *Arch Phys Med Rehabil* 2016;97:273–80.
- Lewis LK, Rowlands AV, Gardiner PA, et al. Small steps: preliminary effectiveness and feasibility of an incremental goal-setting intervention to reduce sitting time in older adults. *Maturitas* 2016;85:64–70.
- Gardner B, Smith L, Lorencatto F, et al. How to reduce sitting time? A review of behaviour change strategies used in sedentary behaviour reduction interventions among adults. *Health Psychol Rev* 2016;10:89–112.
- Orme MW, Weedon AE, Saukko PM, et al. Findings of the chronic obstructive pulmonary Disease-Sitting and exacerbations trial (COPD-SEAT) in reducing sedentary time using wearable and mobile technologies with educational support: randomized controlled feasibility trial. *JMIR Mhealth Uhealth* 2018;6:e84.
- Schulz KF, Altman DG, Moher D, et al. Consort 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
- Cheng SWM, Alison J, Dennis S, et al. A behaviour change intervention to reduce sedentary time in people with chronic obstructive pulmonary disease: protocol for a randomised controlled trial. *J Physiother* 2017;63:182.
- Miller MR, Hankinson J, Brusasco V, ATS/ERS Task force. standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687.
- Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;6:42.
- Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (V1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;46:81–95.
- Byrom B, Rowe DA. Measuring free-living physical activity in COPD patients: deriving methodology standards for clinical trials through a review of research studies. *Contemp Clin Trials* 2016;47:172–84.
- Cheng SWM, Alison J, Stamatakis E, et al. Patterns and correlates of sedentary behaviour accumulation and physical activity in people with chronic obstructive pulmonary disease: a cross-sectional study. *COPD* 2020;17:156–64.
- Haley SM, Fraga-Pinkham MA. Interpreting change scores of tests and measures used in physical therapy. *Phys Ther* 2006;86:735–43.
- Chastin SFM, Winkler EAH, Eakin EG, et al. Sensitivity to change of objectively-derived measures of sedentary behavior. *Meas Phys Educ Exerc Sci* 2015;19:138–47.
- Holland AE, Spruit MA, Troosters T, et al. An official European respiratory Society/American thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1428–46.
- Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. *Respir Med* 1991;85 Suppl B:25–31, discussion 33–37.
- Hibbard JH, Stockard J, Mahoney ER, et al. Development of the patient activation measure (PAM): conceptualizing and measuring activation in patients and consumers. *Health Serv Res* 2004;39:1005–26.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
- Belletiere J, Healy GN, LaMonte MJ, et al. Sedentary behavior and prevalent diabetes in 6,166 older women: the objective physical activity and cardiovascular health study. *J Gerontol A Biol Sci Med Sci* 2019;74:387–95.
- Belletiere J, Winkler EAH, Chastin SFM, et al. Associations of sitting accumulation patterns with cardio-metabolic risk biomarkers in Australian adults. *PLoS One* 2017;12:e0180119.
- McVeigh JA, Winkler EAH, Howie EK, et al. Objectively measured patterns of sedentary time and physical activity in young adults of the Raine study cohort. *Int J Behav Nutr Phys Act* 2016;13:41.
- Saunders TJ, McIsaac T, Douillet K, et al. Sedentary behaviour and health in adults: an overview of systematic reviews. *Appl Physiol Nutr Metab* 2020;45:S197–S21.
- Wijnade L, White T, Andersen LB, et al. Substituting prolonged sedentary time and cardiovascular risk in children and youth: a meta-analysis within the International children's Accelerometry database (ICAD). *Int J Behav Nutr Phys Act* 2019;16:96.
- Chastin SFM, Granat MH. Methods for objective measure, quantification and analysis of sedentary behaviour and inactivity. *Gait Posture* 2010;31:82–6.
- Neuhaus M, Healy GN, Fjeldsoe BS, et al. Iterative development of stand up Australia: a multi-component intervention to reduce workplace sitting. *Int J Behav Nutr Phys Act* 2014;11:21.
- Healy GN, Eakin EG, Lamontagne AD, et al. Reducing sitting time in office workers: short-term efficacy of a multicomponent intervention. *Prev Med* 2013;57:43–8.
- Demeyer H, Burtin C, Hornikx M, et al. The minimal important difference in physical activity in patients with COPD. *PLoS One* 2016;11:e0154587.
- Prince SA, Reed JL, Cote LM, et al. Results of the sedentary intervention trial in cardiac rehabilitation (SIT-CR study): a pilot randomized controlled trial. *Int J Cardiol* 2018;269:317–24.
- Healy GN, Winkler EAH, Owen N, et al. Replacing sitting time with standing or stepping: associations with cardio-metabolic risk biomarkers. *Eur Heart J* 2015;36:2643–9.
- Morgan M. Expanding pulmonary rehabilitation capacity: One size won't fit all. *Thorax* 2017;72:4–5.
- Holland AE, Mahal A, Hill CJ, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. *Thorax* 2017;72:57–65.
- Fitzsimons CF, Kirk A, Baker G, et al. Using an individualised consultation and activPAL™ feedback to reduce sedentary time in older Scottish adults: results of a feasibility and pilot study. *Prev Med* 2013;57:18–20.
- Rosenberg DE, Gell NM, Jones SMW, et al. The feasibility of reducing sitting time in overweight and obese older adults. *Health Educ Behav* 2015;42:669–76.
- Gardner B, Lally P, Wardle J. Making health habitual: the psychology of 'habit-formation' and general practice. *Br J Gen Pract* 2012;62:664–6.
- Cruz J, Brooks D, Marques A, Walk2BActive: a randomised controlled trial of a physical activity-focused behavioural intervention beyond pulmonary rehabilitation in chronic obstructive pulmonary disease. *Chron Respir Dis* 2016;13:57–66.
- Demeyer H, Louvaris Z, Frei A, et al. Physical activity is increased by a 12-week semiautomated telecoaching programme in patients with COPD: a multicentre randomised controlled trial. *Thorax* 2017;72:415.
- Mantoani LC, McKinsty B, McNarry S. Physical activity enhancing programme (PAEP) in COPD – a randomised controlled trial. *Eur Respir J* 2018;52:OA1986.
- Mcewan T, Tam-Seto L, Dogra S. Perceptions of sedentary behavior among socially engaged older adults. *Gerontologist* 2016;56:971–10.
- Weedon AE, Saukko PM, Downey JW. Meanings of sitting in the context of chronic disease: a critical reflection on sedentary behaviour, health, choice and enjoyment. *Qual Res Sport Exer Health* 2019.
- Hall AM, Ferreira PH, Maher CG, et al. The influence of the therapist-patient relationship on treatment outcome in physical rehabilitation: a systematic review. *Phys Ther* 2010;90:1099–110.
- Sparling PB, Howard BJ, Dunstan DW, et al. Recommendations for physical activity in older adults. *BMJ* 2015;350:h100.

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ARTIGO ORIGINAL

Emissão de aerossóis a partir das vias respiratórias: uma análise da geração de aerossóis a partir de sistemas de fornecimento de oxigénio

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RESUMO

Introdução A pressão positiva contínua nas vias respiratórias (CPAP) e o oxigénio nasal de alto fluxo (HFNO) proporcionam um melhor fornecimento de oxigénio e um apoio respiratório para doentes com COVID-19 grave. Atualmente, a CPAP e o HFNO estão designados como procedimentos geradores de aerossóis, apesar dos escassos dados experimentais de alta qualidade. O nosso objetivo foi caracterizar a emissão de aerossóis de HFNO e CPAP e comparar com a respiração, a fala e a tosse.

Materiais e métodos Foram recrutados voluntários saudáveis para respirar, falar e tossir em teatros de fluxo laminar ultra limpos, seguidos pelo uso de CPAP e HFNO. A emissão de aerossóis foi medida usando duas metodologias discretas em simultâneo. Os doentes hospitalizados com COVID-19 registaram a tosse recorrendo à mesma metodologia na unidade de doenças infecciosas.

Resultados Em voluntários saudáveis (n=25 indivíduos; 531 medidas), a CPAP (com filtro de porta de exalação) produziu menos aerossóis do que a respiração, a fala e a tosse (mesmo com grandes fugas nas máscaras faciais >50 L/min). A tosse esteve associada às maiores emissões de aerossóis de qualquer atividade registada. O HFNO esteve associado à emissão de aerossóis. No entanto, esta proveio da máquina. As partículas geradas foram pequenas (<1 µm), passando da máquina, através do doente e para o detetor sem coalescência com o aerossol respiratório, sendo assim pouco provável que transportassem partículas virais. Foram gerados mais aerossóis na tosse de doentes com COVID-19 (n=8) do que em voluntários.

Conclusões Em voluntários saudáveis, a CPAP padrão não humidificada está associada a menor emissão de aerossóis do que a respiração, a fala ou a tosse. A emissão de aerossóis a partir das vias respiratórias não parece ser aumentada por HFNO. Embora as comparações diretas sejam complexas, a tosse parece ser o principal risco gerador de aerossóis de entre todas as atividades medidas.

INTRODUCTION

The WHO describes disease transmission through three routes: physical contact, 'droplet' inhalation (larger particles which settle in a reasonably short distance) or 'airborne' (smaller particles which travel as aerosols on air currents, remaining in the air for longer and distributing over a wide area).¹ SARS-CoV-2, the virus that causes COVID-19, can be transmitted via aerosols with aerosol emission being the putative mode of transmission for many super-spreading events.^{2,3} Although the exact size of aerosol particles responsible for airborne transmission (and the ability of virus to survive in these particles) continues to be debated, it is clear that the dispersion of particles smaller than 5 µm is largely determined by the room ventilation (air exchange) rate, thereby posing a potential risk to include those not in close contact, especially in poorly ventilated areas.⁴ Quantifying the concentration of particles of this size range is therefore critical for understanding the risk of disease transmission.

Key messages

What is the key question?

► Do high-flow nasal oxygen (HFNO) and CPAP produce clinically relevant aerosols?

What is the bottom line?

► In healthy volunteers, CPAP produced no aerosol, and HFNO produced no clinically relevant aerosol, while coughing was associated with significant aerosol production.

Why read on?

► Management of patients in respiratory failure with potentially infectious pathogens remains a complex area with little evidence. This paper provides some of the first high-quality data on potential risks associated with aerosol emissions.

Traditionally, medical procedures are deemed as 'aerosol generating' when there is a perceived risk of increased generation of aerosol from the patients' mucosa or respiratory tract compared with normal breathing, exposing staff and others in the vicinity to risk of inhalation of aerosolised airborne virus. For these aerosol-generating procedures (AGPs), an extra set of infection control precautions are mandated.⁵⁻⁷ These additional precautions often involve: segregating these patients from others, changing personal protective equipment to include FFP3 (or N95) masks that limit aerosol inhalation rather than fluid-resistant surgical masks (FRSMs), ensuring adequate ventilation, and allowing 'fallow' time between procedures to allow aerosol to disperse.

These mitigation strategies have significant impact on healthcare capacity, costs and potential harms; it is therefore critical to accurately identify whether these procedures truly do generate aerosol.⁸ Our aim was to identify whether procedures generate appreciable aerosol and whether the aerosol number concentration is lower than that generated by a cough. If so, the AGP is likely of low risk and misclassified.

Oxygen delivery and respiratory support including continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO) are used for the management of hypoxaemic respiratory failure complicating COVID-19 pneumonia. CPAP and HFNO are currently deemed AGPs by both the WHO and Public Health England (now the UK Health Security Agency), although the evidence for these recommendations is sparse.^{5,7,9,10} Current guidance stipulates the need to cohort these patients

and universal FFP3 usage in any setting where a patient is receiving CPAP or HFNO. However, universal FFP3 usage is not currently recommended when caring for general inpatients with COVID-19, despite the potential risks from breathing, speaking and coughing in this setting.

In this study, we set out to quantify aerosol generation in both CPAP and HFNO and compare it with breathing, speaking and coughing without these supports.

METHODS

Full technical methods are in the online supplemental appendix S1. In brief, healthy volunteers were recruited in ultra-clean, laminar flow operating theatres and underwent a protocolised set of testing (breathing, speaking and coughing) under different oxygen delivery systems and without respiratory support. Participants were instructed to perform three voluntary coughs into the measuring funnel, moving their head away from the funnel after each cough.

Aerosol measurements were taken simultaneously by two separate devices, the Aerodynamic Particle Sizer (APS) and Optical Particle Sizer (OPS) (both manufactured by TSI), via a 3D-printed funnel and through 0.45 m of conductive silicone tubing. Both devices were included as they work on differing technologies and are able to detect aerosols of differing sizes (APS, 0.5–20 µm; OPS, 300 nm–10 µm).

Aerosol number concentrations were compared via Wilcoxon rank-sum tests on paired data, with a Bonferroni adjusted *p* value for multiple comparisons. Speaking and breathing were assessed as the average number concentration of aerosol during the activity, whereas the peak number concentration was recorded for coughing. Given the non-parametric nature of the data, we report median and IQR for all results.

COVID-19 Patients were recruited on the infectious disease ward and had measurements of cough taken using the same methodology. Each measurement was taken at the bedside in single occupancy negative pressure rooms that draw clean air from the ventilation system above. However, background aerosol concentration was significantly higher than in the operating theatres, precluding reliable measurements of breathing and speaking.

RESULTS

Overall results and demographics

Thirty-three participants were recruited, of which 25 were healthy volunteers, and 8 were hospitalised patients with COVID-19. Thirteen (57%) of the volunteers were female, with a median age of 35 years (IQR 32–40 years), weight of 72 kg (IQR 64–79 kg), height of 1.74 m (IQR 1.64–1.79 m) and body mass index (BMI) of 23.6 kg/m² (IQR 22.0–25.5 kg/m²).

Hospitalised patients with COVID-19 were older (mean age 55 years, IQR 49–59 years), with five men and three women. Height and weight were available for two patients: both were 170 cm tall; one weighed 85 kg (BMI: 29.4 kg), the other weighed 139 kg (BMI: 48.1 kg).

Volunteer aerosol emission

Table 1 describes the number of times each activity was performed, and on how many volunteers, alongside aerosol emission for each activity. The number of activities does not match the number of participants, as some volunteers (*n*=6) repeated the assessments on a different day to check repeatability, and some measurements were only performed on certain participants.

Correlation between the APS and OPS devices was high (*r*=0.98 unlogged, *r*=0.80 logged), despite the differing methodologies. Therefore, further analysis reports the APS figures in the text only, except where stated.

Figure 1A,B,C shows the aerosol number concentrations of each activity for volunteers, as reported by the APS (see online supplemental figure S4 for the OPS) and shows the clear variation in aerosol concentrations as well as the typical log-normal distribution. For baseline measurements, speaking produced more aerosol than breathing, and wearing an FRSM significantly reduced measured aerosol emission during both speaking (median 0.88 vs 0.03 particles/cm³, *p*<0.0001) and coughing (median 1.52 vs 0.12 particles/cm³, *p*<0.0001).

Continuous positive airway pressure

As shown in figure 1, aerosol emission sampled from participants receiving CPAP is greatly reduced compared with baseline

measurements while breathing, speaking and coughing. Even with a large induced face mask air leak (>50 L/min), the aerosol emission measured over that leak during coughing was lower than in participants not receiving CPAP (0.12 vs 1.52 particles/cm³; *p*<0.0001). At the filtered CPAP exit port, the aerosol emission was negligible and much reduced compared with those emitted during breathing, speaking or coughing in ambient room air (*p*<0.0001 for all comparisons).

Removal of the CPAP mask was associated with some aerosol emission, but this was significantly less than a cough in a healthy volunteer (peak of 0.36 particles/cm³ vs 1.52 particles/cm³, *p*<0.0001). In summary, CPAP was not associated with increased aerosolisation, but conversely was associated with much lower recorded aerosol number concentrations across all settings.

High-flow nasal oxygen

Assessment of aerosol emission from HFNO was complex. Our initial experiment used a single HFNO machine, with details described below.

HFNO was associated with increased aerosol number concentrations compared with breathing ambient room air (median aerosol in HFNO 30 L/min, 0.277 particles/cm³; HFNO 60 L/min, 1.86 particles/cm³; ambient air 0.03 particles/cm³, *p*<0.0001 for all comparisons).

Higher flow rates (60 L/min) were associated with higher reported aerosol number concentrations than lower flow rates (30 L/min) for speaking (1.86 vs 0.246 particles/cm³, *p*<0.001), breathing (1.86 vs 0.277 particles/cm³, *p*<0.001), but not coughing (3.01 vs 2.96 particles/cm³, *p*=0.002), nor coughing with a surgical face mask (0.63 vs 0.24 particles/cm³, *p*=0.007), as both did not meet the Bonferroni corrected threshold (*p*=0.0004).

On review, the characteristics of the aerosol emissions during HFNO were not consistent with production of aerosol from the respiratory tract or mucosal surfaces, and aerosol was emitted even when the machine was unattached to the patient. We therefore performed a set of experiments to assess the source of this aerosol and their size distribution, with full experimental detail and results in the online supplemental appendix (see 'Aerosol Concentrations Generated by HFNO' and online supplemental figures S5–S8).

Importantly, we found that aerosol emission varied greatly among machines (two of four tested machines did not generate any aerosol), and that the size distribution of aerosol was not consistent with aerosol from the respiratory tract.

Patients with COVID-19 versus healthy volunteers

In total, eight patients were recruited with COVID-19. Demographics of these patients are recorded in online supplemental table S2. Measurement of aerosol concentrations generated by these patients was technically difficult due to the acute clinical environment, infection control requirements and the room's higher background aerosol number concentration, necessitating high efficiency particulate air (HEPA) filtration to reduce this concentration and allow respiratory aerosol measurements. Four participants were on standard, low-flow nasal oxygen, while the others were breathing room air. For four participants, the background aerosol concentration in the room was higher than median concentrations generated by speaking and breathing measured in the ultra-clean theatres, so we only report the aerosol emission from coughing.

Figure 2 shows the aerosol emission recorded during coughing for both patients and volunteers. Compared with volunteers, patients with COVID-19 had higher aerosol emission when coughing (*n*=8; 10.5 vs 1.52 particles/cm³, *p*=0.002) and when coughing wearing an FRSM, although due to low numbers neither met Bonferroni correction (*n*=3, 0.94 vs 0.12 particles/cm³, *p*=0.03).

Importantly, the size distribution of aerosol particles in patients with COVID-19 was very similar to healthy volunteers (online supplemental figure S4). Breathing, speaking and coughing all generated aerosol particles in a log-normal size distribution with the peak in the 0.5–1 µm diameter range, consistent with previous reports of the size distribution of respiratory aerosol emissions.^{11–14} This supports the use of healthy volunteers as proxies for patients infected with SARS-CoV-2.

Table 1 Aerosol emission produced across all activities in healthy volunteers

Oxygen delivery	Activity	Number of measurements	Aerosol emission (APS, particles/cm ³)*	Aerosol emission (OPS, particles/cm ³)*
Nil	Breathing	25	0.044 (0.022–0.08)	0.042 (0.023–0.125)
Nil	Speaking	25	0.088 (0.064–0.212)	0.121 (0.075–0.237)
Nil	Speaking with FRSM	23	0.03 (0.016–0.131)	0.038 (0.013–0.166)
Nil	Cough	25	1.52 (0.601–3.06)	2.14 (0.49–4.382)
Nil	Cough with FRSM	23	0.12 (0.06–0.555)	0.15 (0.06–0.57)
HFNO (60 L/min)	Breathing	20	1.861 (1.54–3.458)	2.921 (2.127–5.044)
HFNO (60 L/min)	Speaking	20	1.855 (1.201–2.359)	2.571 (1.65–3.255)
HFNO (60 L/min)	Cough	21	3.006 (2.597–5.525)	4.25 (3.011–6.41)
HFNO (60 L/min)	Cough with FRSM	10	0.63 (0.21–2.189)	0.75 (0.375–1.89)
CPAP at 15 mm Hg	Breathing sampling at area of greatest natural leak	20	0.013 (0.009–0.024)	0.012 (0.009–0.035)
CPAP at 15 mm Hg	Breathing sampling at exit port	20	0.002 (0–0.006)	0 (0–0.002)
CPAP at 15 mm Hg	Speaking sampling at exit port	8	0 (0–0.002)	0.001 (0–0.002)
CPAP at 15 mm Hg	Cough sampling at exit port	19	0.04 (0.01–0.06)	0.04 (0–0.105)
CPAP at 15 mm Hg	Cough sampling at leak	17	0.12 (0.06–0.72)	0.21 (0–0.99)
CPAP at 15 mm Hg	Removing CPAP mask	6	0.36 (0.195–0.57)	0.36 (0.27–0.6)

*This is the median IQR across individuals; average particles/cm³/s for continuous activities, peak particles/cm³ for sporadic activities. APS, Aerodynamic Particle Sizer; FRSM, fluid-resistant surgical mask; HFNO, high-flow nasal oxygen; OPS, Optical Particle Sizer.

Repeated measurements

For a subset of healthy volunteers (n=6), repeated measurements were made 1 month later. In total, there were 116 measurements repeated, (76 APS; 40 OPS). Correlation with the original measurement was moderate (r=0.71 on logged data), although this was driven by strong correlation in breathing (r=0.81), rather than speaking (r=0.17 on logged data) and coughing (r=0.38 on logged data) suggesting aerosol concentrations from breathing are relatively consistent for any individual recorded over a period of time, given the limitations inherent in the small numbers. In general, measurements on the second visit were marginally lower, which may represent slight differences in the experimental set-up.

Online supplemental figures S1 and S2 show these data, coloured by participant (S1) and activity (S2). Online supplemental figure S3 shows a Bland-Altman plot of this relationship.

DISCUSSION

Summary

This study comprehensively characterised the aerosol generation during standard CPAP and HFNO procedures, as compared with normal breathing, speaking and coughing. CPAP delivered by face mask with exhalation filter was actually associated with lower aerosol number concentrations, even when large air leaks created around the CPAP face mask (>50 L/min) reflect the disruptions in CPAP of routine clinical care. For HFNO, aerosol concentrations were higher than baseline recordings. However, this additional aerosol was only present in some machines and largely disappeared with the use of a filter between the device and the patient. The size distribution of aerosol was unchanged when measured directly from the device or when attached to a patient, further supporting a non-biological origin.

Therefore, CPAP and HFNO should not be deemed AGPs, and provide no greater risk to healthcare staff relative to patients breathing, coughing and talking.

This is the first study to report on aerosol emission from patients with active COVID-19, with previous work on primates only.¹⁵ While the data suggest that peak aerosol concentrations from coughs are higher than those from healthy volunteers without COVID-19, the background aerosol concentration on the ward was too high to report data on speaking and breathing.

Our analysis shows that a single cough generates at least 10-fold more aerosol particles at the peak concentration relative to the mean concentration for speaking or breathing (median concentrations of 1.52 particles/cm³, 0.088 particles/cm³ and 0.03 particles/cm³ for cough, speaking and breathing, respectively, p<0.0001 for all comparisons).

cm³ for cough, speaking and breathing, respectively, p<0.0001 for all comparisons).

In summary, our data (in concert with prior research on AGPs,^{9,12} epidemiological studies showing lower risk to staff working in intensive care^{16–20} and with viral loads higher earlier in infection, when patients are more often on the general wards²¹) suggest that risk of SARS-CoV-2 infection is not due to CPAP or HFNO generating infective aerosols. This has implications for infection and prevention control policy since aerosol generation appears greatest from patients with COVID-19 who are coughing.

Strengths and weaknesses

This study has multiple strengths. First, it was performed in ultra-clean laminar flow theatres, with very low aerosol background concentrations, allowing accurate quantification and attribution of aerosol emission. Second, the strong correlation between both aerosol measurement modalities provides confidence that the aerosol measurements are reliable. Third, repeated measurements and the recruitment of patients with active COVID-19 allow greater interpretation of clinical implications. Finally, the protocol reflects usual clinical care and is directly translatable to the health service delivery.

However, there are some important weaknesses. First, measurement methodology employed by the APS and OPS uses relatively low flow rates (1 L/min and 5 L/min, respectively). These mean that very short, high-impact aerosol emissions (eg, cough) may be hard to quantify. However, this applies to all APS and OPS technology, and does not limit relative comparison between oxygen delivery systems. Second, our assessment of patients with COVID-19 is limited, as we only recruited hospitalised patients and were only able to reduce background aerosol emission enough to reliably measure cough. Although these data are limited, they suggest that aerosol emission from patients with COVID-19 is likely to be higher than in volunteers, and underlines the difficulties in making these measurements in real patients.

It is important to note that the majority of our measurements (like in all other studies so far) come from healthy volunteers. It is likely that demographics (weight, height, age) have some impact on aerosol emission, and therefore some caution must be taken in extrapolating the raw data on aerosol emission, although we have no reason to suspect the changes in aerosol emission seen with delivery systems would dramatically change.

Finally, our non-humidified CPAP system uses full face masks with exhalation filters, which are standard care in our hospital and

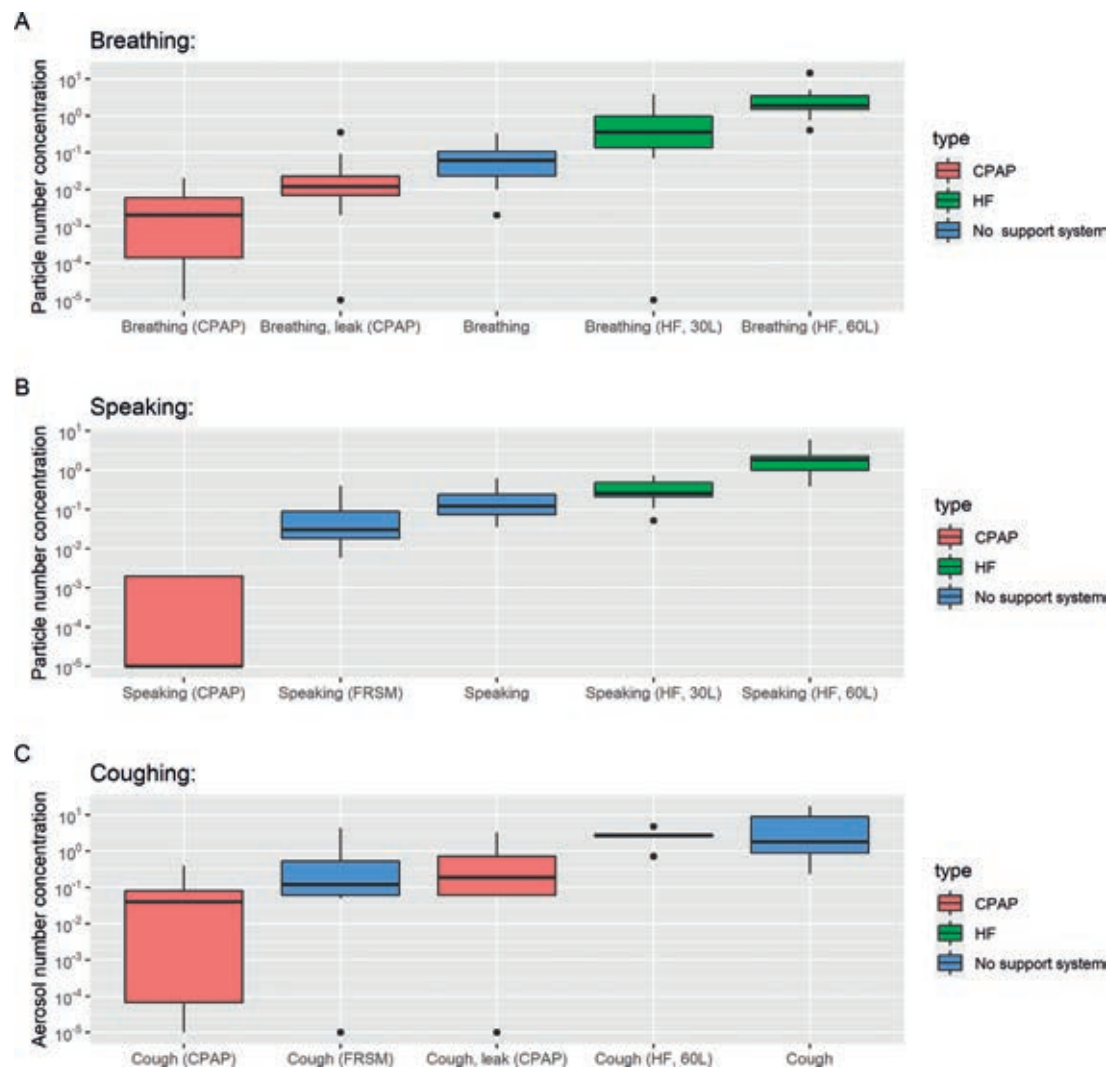


Figure 1 The aerosol number concentration sampled by an APS during baseline activities, CPAP or HFNO, reporting the mean concentration sampled during breathing (A) and speaking (B), and reporting the peak concentration sampled during coughs (C). Boxplots represent median and IQR. APS, Aerodynamic Particle Sizer; FRSM, fluid-resistant surgical mask; HFNO, high-flow nasal oxygen.

in many NHS hospitals outside critical care, following national policy at the start of the pandemic.²² We cannot extrapolate to CPAP face masks without exhalation filters, although aerosol concentrations recorded from the face mask leak (unfiltered) were less than coughing without CPAP. As our system was unhumidified, we also cannot generalise to systems that use external humidification.

Similarly, the variability within the HFNO oxygen system used suggests that recorded aerosol emission may vary with device. As we only tested one manufacturer for each device, we cannot be sure that aerosol emission would differ with other manufacturers. However, as the mechanism of humidification and pressure generation is similar across different HFNO devices, it is likely that clinically relevant aerosol emission (eg, from the respiratory tract) is similar across devices. It is important to note that we cannot extrapolate to humidified CPAP devices, although we note the use of non-humidified CPAP is common in the management of patients with COVID-19 across many institutions.

We have chosen not to correct the reported particle concentrations sampled during each procedure to account for the effect of dilution by the airflow because the relative flow rate between each subject's different exhalation events compared with CPAP and HFNO is ill-defined. Thus, the uncorrected aerosol number concentrations as sampled by the APS and OPS do not represent the absolute quantity of particles generated by each activity, but can be used as a measure of the risk to a healthcare worker in the vicinity of the activity.

As activities such as coughing are forceful and short lived, these were analysed separately to the continuous activities (eg, breathing): short, transient activities are observed as a rapid rise in the reported

number concentration followed by a decay over a few sample measurements (typically equivalent to 10–15 s for a cough) as the aerosol dissipates from the sampling funnel and is diluted by the clean room air. While reporting the intensive property of concentration allows us to compare relative yields from AGPs, it is important to note that estimating absolute yields or fluxes (extensive properties) requires knowledge of the volumetric flow rates for the gas in which the aerosol is dispersed. These present an additional challenge to measure. Although it is possible to report the absolute number of particles counted by the instruments (given we know their sampling volumetric flow rates), we cannot conclude that this is equivalent to the total aerosol yield without knowing the volumetric flow rate at aerosol source (ie, participant's mouth).

Comparisons with previous literature

There are few published studies of aerosol generation from oxygen delivery systems and respiratory support. The most similar study was performed by Gaeckle *et al*, which measured protocolised respiratory support systems in volunteers.⁹ A similar protocol was used, although they also measured simple nasal cannulae and changes in respiration. Importantly, they reported a background aerosol concentration of ~ 0.060 particles/cm³ (compared with zero under laminar flow), higher than we report for many activities (including breathing and speaking with an FRSM). As well as a high background, the aerosol number concentration was highly variable in their study (see figure 4 and E3 from reference 11, and figure 3 here for comparison). This variability makes reporting accurate aerosol concentrations for short events (eg, a cough) challenging, as we noted in recruiting our patients with COVID-19.

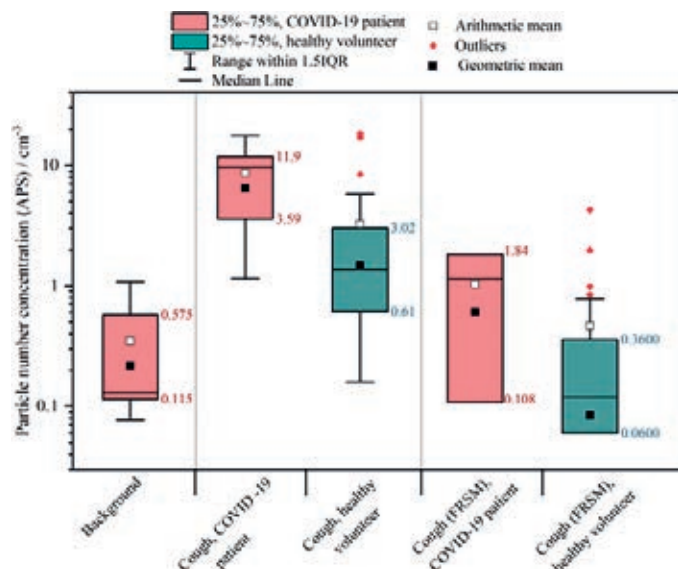


Figure 2 Box and whisker plot comparing the aerosol sampled by an APS when coughing in healthy subjects and by PCR-positive patients with COVID-19. APS, Aerodynamic Particle Sizer; FRSM, fluid-resistant surgical mask.

Consistent with our study, Gaeckle *et al* reported non-invasive ventilation to be non-aerosol generating. However, by contrast, they did not identify increased aerosol emission with HFNO. A very recent study, performed by Wilson *et al*,²³ measured aerosol counts in 10 healthy volunteers in a chamber, attempting to collect all exhaled aerosol. Similar to our study, they found coughing produced large amounts of aerosol compared with breathing and speaking. However, in contrast to our study, they identified small increases in aerosol emission with both CPAP (2.6-fold with single circuit) and HFNO (2.3-fold) with normal breathing. However, during exertion, they identified a reduction in aerosol emission with both of these therapies compared with breathing unaided. As Wilson *et al* comment (on our preprint), the differing results likely reflect different approaches to measuring and recording peak and average aerosol emission, but the underlying results from both studies

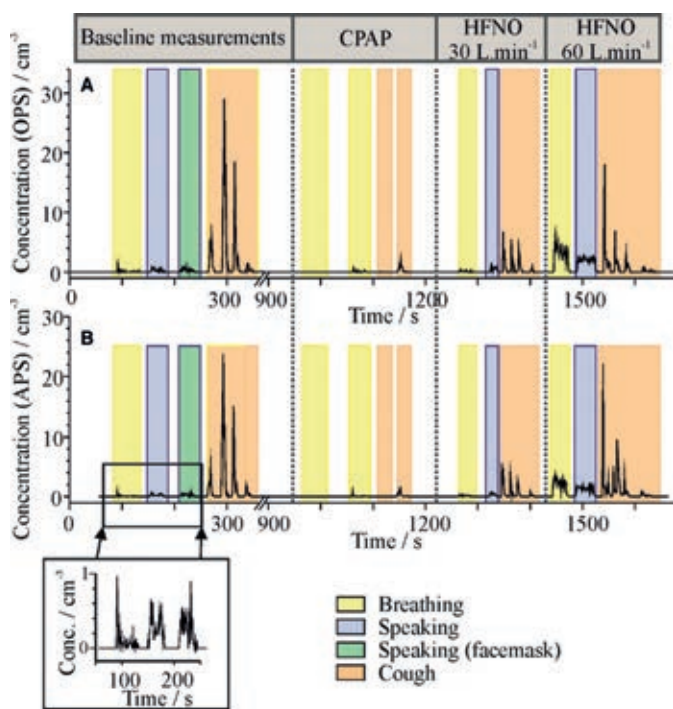


Figure 3 Example of the time series of OPS (A) and APS (B) number concentrations sampled during a measurement of one healthy subject performing baseline activities, followed by CPAP then HFNO. APS, Aerodynamic Particle Sizer; HFNO, high-flow nasal oxygen; OPS, Optical Particle Sizer.

suggest that coughing represents a more significant source of aerosol than respiratory supports such as CPAP and HFNO.

The analysis presented in this paper, along with other work from our group identifying that intubation does not also generate significant aerosol,¹² suggest that the current infection and prevention control aerosol risk stratification strategies based on procedures rather than time spent in contact with patients coughing with COVID-19 may be misplaced.

Implications for clinical practice and policy

This study strongly supports re-evaluation of guidance removing CPAP as a high-risk AGP, with implications for more efficient delivery of NHS services. However, given that patients who receive acute respiratory support for COVID-19 are often acutely unwell and cough, the risk of aerosolisation of SARS-CoV-2 may be significant, complicating the policy changes. This work supports a re-evaluation of focusing solely on AGPs as potential risky events, and a shift towards focusing on the patient.

CONCLUSIONS

Non-humidified CPAP delivered via a filtered mask actually reduces aerosol emission compared with normal breathing. HFNO does generate additional aerosol, however this aerosol is generated from the machine and not the patient, and is unlikely to pose extra clinical risk given the size ($<1\mu\text{m}$). Cough appears to generate significant aerosols in a size range compatible with airborne transmission of SARS-CoV-2. Policy around aerosol generation and infection control should be updated to reflect these adjusted risks.

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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. KW provided expert opinion and analysis on respiratory support. JWD is the guarantor.

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Competing interests None declared.

Patient consent for publication Not required.

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).

Provenance and peer review Not commissioned; externally peer reviewed.

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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REFERENCES

1. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. Available: <https://www.who.int/publications/item/10665-331495> [Accessed 1 Apr 2021].
2. Hamner L, Dubbed P, Caproni L, et al. High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice - Skagit County, Washington, March 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:606-10.
3. Liu Y, Ning Z, Chen Y, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. *Nature* 2020;582:557-60.
4. Klompas M, Baker MA, Rhee C. Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. *JAMA* 2020;324:441-2.
5. Public Health England. COVID-19 infection prevention and control guidance: aerosol generating procedures, 2020. Available: <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control/covid-19-infection-prevention-and-control-guidance-aerosol-generating-procedures> [Accessed 1 Apr 2021].
6. Public Health England. COVID-19: personal protective equipment use for aerosol generating procedures, 2020. Available: <https://www.gov.uk/government/publications/covid-19-personal-protective-equipment-use-for-aerosol-generating-procedures> [Accessed 24 Jun 2021].
7. World Health Organization. Pandemic and epidemic diseases, world Health organization. Infection prevention and control of Epidemic and Pandemic-prone acute respiratory infections in health care: who guidelines. Geneva: Pandemic and Epidemic Diseases, World Health Organization, 2014.
8. Klompas M, Baker M, Rhee C. What is an Aerosol-Generating procedure? *JAMA Surg* 2021;156:113-4.
9. Gaeckle NT, Lee J, Park Y, et al. Aerosol generation from the respiratory tract with various modes of oxygen delivery. *Am J Respir Crit Care Med* 2020;202:1115-24.
10. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. *Eur Respir J* 2019;53. doi:10.1183/13993003.02339-2018. [Epub ahead of print: 11 Oct 2019].
11. Asadi S, Weder AS, Cappa CD, et al. Aerosol emission and superspreading during human speech increase with voice loudness. *Sci Rep* 2019;9:2348.
12. Brown J, Gregson FKA, Shrimpton A, et al. A quantitative evaluation of aerosol generation during tracheal intubation and extubation. *Anaesthesia* 2021;76:174-81.
13. Johnson GR, Morawski L, Ristovski ZD, et al. Modality of human expired aerosol size distributions. *J Aerosol Sci* 2011;42:839-51.
14. Alsted M, Matamis A, Bohlin R, et al. Exhaled respiratory particles during singing and talking. *Aerosol Sci Technol* 2020;54:1245-8.
15. Edwards DA, Aussel D, Langer R. Exhaled aerosol increases with COVID-19 infection, and risk factors of disease symptoms severity. *bioRxiv* 2020.
16. Jones CR, Hamilton FW, Thompson A, et al. SARS-CoV-2 IgG seroprevalence in healthcare workers and other staff at North Bristol NHS trust: a sociodemographic analysis. *J Infect* 2021;82:e24-7.
17. Eyre DW, Lumley SE, O'Donnell J, et al. Differential occupational risks to healthcare workers from SARS-CoV-2 observed during a prospective observational study. *Elife* 2020;9. doi:10.7554/eLife.60675. [Epub ahead of print: 21 Oct 2020].
18. Martin CA, Patel P, Goss C, et al. Demographic and occupational determinants of anti-SARS-CoV-2 IgG seropositivity in hospital staff. *J Public Health* 2020. doi:10.1093/pubmed/kdab199. [Epub ahead of print: 16 Nov 2020].
19. Shah ASV, Wood R, Gribben C, et al. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households nationwide linkage cohort study. *BMJ* 2020;371:m3582.
20. Shields A, Padellaro SE, Perez-Toledo M, et al. SARS-CoV-2 seroprevalence and asymptomatic viral carriage in healthcare workers: a cross-sectional study. *Thorax* 2020;75:1089-94.
21. Cevik M, Tate M, Lloyd O, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2021;2:e13-22.
22. England NHS. Guidance for the role and use of non-invasive respiratory support in adult patients with coronavirus (confirmed or suspected). Available: <https://amhp.org.uk/app/uploads/2020/03/Guidance-Respiratory-Support.pdf>
23. Wilson NM, Marks GB, Eckhardt A. The effect of respiratory activity, ventilatory therapy and facemasks on total aerosol emissions. *bioRxiv* 2021.

ARTIGO ORIGINAL

A falta de ar ao longo de gerações: resultados do estudo geracional RHINESSA

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RESUMO

Antecedentes A falta de ar é uma das principais causas de sofrimento e incapacidade a nível global. O sintoma está relacionado com múltiplos fatores, incluindo asma e função pulmonar, que são influenciados por fatores hereditários. Não existe nenhum estudo que tenha avaliado a herança potencial da falta de ar ao longo das gerações.

Métodos Analisámos a associação entre a falta de ar dos progenitores e dos seus descendentes no estudo geracional de Saúde Respiratória no Norte da Europa, Espanha e Austrália. Os dados sobre progenitores e descendentes com idades ≥18 anos em 10 centros de estudo em sete países incluíram demografia, falta de ar auto-reportada, asma, depressão, tabagismo, nível de atividade física, Índice de Massa Corporal medido e espirometria. Os dados foram analisados com recurso a regressão logística multivariável, considerando a agregação dentro dos centros e entre irmãos.

Resultados Foram incluídos um total de 1720 progenitores (idade média na avaliação de 36 anos, 55% mães) e um total de 2476 descendentes (média de 30 anos, 55% filhas). A falta de ar foi reportada por 809 (32,7%) progenitores e 363 (14,7%) descendentes. Os fatores independentemente associados com a falta de ar nos progenitores e descendentes incluíram obesidade, tabagismo corrente, asma, depressão, função pulmonar reduzida e sexo feminino. Após ajustar para potenciais confundidores, os progenitores com falta de ar apresentavam maior probabilidade de ter descendentes com falta de ar, OR ajustado 1,8 (95% IC 1,1 a 2,9). A associação não sofreu modificações devido ao sexo do progenitor ou dos descendentes.

Conclusão Os progenitores com falta de ar mostraram maior probabilidade de ter filhos que desenvolveram falta de ar, depois de ajustar para asma, função pulmonar, obesidade, tabagismo, depressão e sexo feminino em ambas as gerações. Os componentes hereditários da falta de ar carecem de ser mais explorados.

INTRODUCTION

Breathlessness related to daily activities is common in many populations, affecting 15%–45% of middle-aged and older people in the community.^{1–3} Physical disability due to activity-related breathlessness, measured using the modified Medical Research Council (mMRC) scale,⁴ is associated with major adverse health outcomes including impaired quality of life^{1,5,6} and earlier death.^{7,8}

Breathlessness in the population is related to multiple factors including cardiorespiratory disease, obesity, deconditioning, mental state, occupational and environmental exposures, and early life factors.^{1–3,9–12} Ventilatory capacity, assessed using FEV₁ and FVC, is related to breathlessness. This could explain why breathlessness is more prevalent in women, having smaller lungs and airways compared with men.^{13–15} Furthermore, airflow obstruction is strongly related to increased breathlessness,^{1,2,12–15} with asthma being an especially prevalent risk factor at younger ages.¹⁶

Key messages

What is the key question?

► Does breathlessness cluster across generations?

What is the bottom line?

► Breathlessness was nearly doubled in offspring of parents with breathlessness, even when adjusting for factors associated with breathlessness in both generations (obesity, smoking, depression, asthma, lower lung function and female sex).

Why read on?

► This is the first large population study evaluating breathlessness across generations which supports potential heritability of breathlessness.

While heritability in asthma^{17–19} and lung function^{20–22} is well established, it is unknown whether breathlessness clusters across generations. No study has evaluated whether parents with breathlessness are more likely to have offspring with breathlessness or the potential factors underpinning any such association. Clustering of breathlessness across the generations is conceivable, as several determinants of breathlessness are known to be at least partly hereditary, including level of lung function,^{20,21} physical activity,²³ obesity and body fat composition, and asthma.^{17–19}

The primary aim of this study was to evaluate whether parents' breathlessness was a risk factor for offspring breathlessness, when accounting known risk factors for breathlessness in both generations. Second, we aimed to explore potential sex-specific patterns by evaluating if associations in breathlessness across generations were modified by the sex of the parent and/or the offspring.

METHODS

Study design and population

This was an analysis within the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) generation study.²⁴ Parents were identified from the European Community Respiratory Health Survey (ECRHS, www.ecrhs.org). In 10 ECRHS study centres, data on their offspring were obtained for the RHINESSA study (www.rhinessa.net). The analysis database comprised one parent (mother or father) and one or more offspring for each parent. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.²⁵

Table 1 Characteristics of offspring (n=2476) and parents (n=1720) by the presence of offspring breathlessness

Factor	Offspring without breathlessness	Offspring with breathlessness	P value
Offspring factors			
N	2113	363	
Age, mean (SD)	29.8 (7.7)	30.5 (7.4)	0.074
Daughter	1130 (53.5%)	223 (61.4%)	0.005
Asthma	285 (13.6%)	198 (54.8%)	<0.001
BMI, mean (SD)	24.4 (4.5)	25.5 (5.3)	<0.001
BMI category (kg/m ²)			<0.001
<20	246 (11.6%)	30 (8.3%)	
20–<25	1070 (50.6%)	159 (43.8%)	
25–<30	533 (25.2%)	103 (28.4%)	
≥30	199 (9.4%)	57 (15.7%)	
Missing	65 (3.1%)	14 (3.9%)	
Current smoker	242 (11.6%)	77 (21.6%)	<0.001
Pack-years of smoking, median (IQR)	0 (0–0.1)	0 (0–3.0)	<0.001
Depression	72 (10.0%)	33 (26.6%)	<0.001
Exercise level			0.035
Almost every day	466 (22.1%)	64 (17.6%)	
2–3 times a week	844 (39.9%)	130 (35.8%)	
Once a week	330 (15.6%)	67 (18.5%)	
Less than once a week	306 (14.5%)	65 (17.9%)	
Never	125 (5.9%)	29 (8.0%)	
Missing	42 (2.0%)	8 (2.2%)	
FEV ₁ , mean (SD)	4.0 (0.8)	3.7 (0.8)	<0.001
FVC, mean (SD)	4.7 (1.0)	4.5 (1.0)	0.022
FEV ₁ /FVC, mean (SD)	0.8 (0.1)	0.8 (0.1)	0.002
Parent factors			
Age, mean (SD)	35.7 (6.2)	36.5 (5.8)	0.021
Mother	1121 (53.1%)	210 (57.9%)	0.090
Breathlessness	651 (30.8%)	158 (43.5%)	<0.001
mMRC breathlessness score			0.008
0	1789 (84.7%)	286 (78.8%)	
1	246 (11.6%)	51 (14.0%)	
≥2	76 (3.6%)	24 (6.6%)	
Missing	2 (0.1%)	2 (0.6%)	
Asthma	302 (15.8%)	71 (23.4%)	0.001
Depression	190 (14.2%)	47 (18.7%)	0.069
BMI, mean (SD)	24.7 (4.3)	25.3 (4.6)	0.016
BMI category (kg/m ²)			0.064
<20	155 (7.3%)	19 (5.2%)	
20–<25	1058 (50.1%)	165 (45.5%)	
25–<30	618 (29.2%)	123 (33.9%)	
≥30	185 (8.8%)	40 (11.0%)	
Missing	97 (4.6%)	16 (4.4%)	
FEV ₁ , mean (SD)	3.7 (0.8)	3.5 (0.7)	<0.001
FEV ₁ % of predicted, mean (SD)	112.4 (19.0)	107.2 (19.6)	<0.001
FVC, mean (SD)	4.6 (1.0)	4.4 (1.0)	0.006
FVC % of predicted, mean (SD)	110.1 (15.4)	108.6 (16.9)	0.17

Continued

Table 1 Continued

Factor	Offspring without breathlessness	Offspring with breathlessness	P value
FEV ₁ /FVC, mean (SD)	0.8 (0.1)	0.8 (0.1)	<0.001
FEV ₁ /FVC<0.7	114 (5.6%)	33 (9.5%)	0.006
Current smoker	667 (34.5%)	121 (37.8%)	0.25
Pack-years of smoking, median (IQR)	0 (0–12.6)	1.5 (0–15.5)	0.070
Highest education			0.11
Primary	187 (8.8%)	40 (11.0%)	
Secondary	651 (30.8%)	105 (28.9%)	
University	748 (35.4%)	105 (28.9%)	
Missing	527 (24.9%)	113 (31.1%)	
Exercise level			0.033
Every day	135 (6.4%)	26 (7.2%)	
4–6 times a week	400 (18.9%)	59 (16.3%)	
2–3 times a week	599 (28.3%)	88 (24.2%)	
Once a week	167 (7.9%)	22 (6.1%)	
Once a month	128 (6.1%)	29 (8.0%)	
Less than once a month	128 (6.1%)	24 (6.6%)	
Never	258 (12.2%)	64 (17.6%)	
Missing	298 (14.1%)	51 (14.0%)	

Data presented as frequency (%) or mean (SD) unless otherwise indicated.
 BMI, Body Mass Index; mMRC, modified Medical Research Council.

Parents

The ECRHS study surveyed population-based random samples of adults aged 20–44 years in 1992 (~3000 per research centre) in 56 study centres across 25 countries.^{20,21} This study includes the cohort from 10 study centres in Northern Europe, Spain and Australia with clinical examinations including spirometry. These 10 centres were Aarhus (Denmark); Bergen (Norway); Gothenburg, Uppsala and Umeå (Sweden); Reykjavik (Iceland); Tartu (Estonia); Huelva and Albacete (Spain); and Melbourne (Australia). The remaining 46 centres did not examine the participants' offspring and were consequently not part of the RHINESSA generation study.

Offspring

All adult offspring (≥18 years) of parents from the following ten ECRHS centres were invited to complete questionnaires and participate in clinical examination including spirometry in 2013–2015.²⁴ Spirometry was performed using standardised protocols similar to those used for investigation of their parents.²⁴ The questionnaires were web-based in all centres except for the Swedish centres, where postal questionnaires were used. In total, 33.5% of the invited adult offspring participated in the study, with response rates varying across centres from 18.6% in Tartu to 73.7% in Melbourne.²⁶

The current analysis is based on this adult offspring study of men and women aged ≥18 years with physiological data including spirometry. Exclusion criteria for the present analysis were inability to walk for other reasons than breathlessness (as most breathlessness is related to physical activity) and missing data on breathlessness in parents or offspring.

Assessments and definitions

Breathlessness was defined similarly in parents and offspring as the self-report of any of the following symptoms during the last 12 months: (1) breathlessness when having wheezing and whistling in the chest, (2) attack of shortness of breath when at rest, (3) attack of shortness of breath following strenuous activity or (4) being woken by an attack of shortness of breath. Breathlessness and other factors were assessed at the first available data point for parents (ECRHS I)

Table 2 Factors associated with breathlessness in parents

Parental factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 1 year)	1.0 (1.0 to 1.0)	1.0 (0.9 to 1.0)
Female versus male	0.9 (0.8 to 1.1)	0.5 (0.3 to 0.8)
Body Mass Index (kg/m ²)		
<20	1.0 (0.7 to 1.4)	1.2 (0.6 to 2.3)
20–<25	1 (ref)	1 (ref)
25–<30	1.2 (1.0 to 1.4)	1.5 (0.7 to 2.9)
≥30	1.7 (1.3 to 2.39)	2.3 (1.0 to 5.1)
Asthma	15.1 (11.1 to 20.4)	16.3 (10.1 to 26.1)
Current smoker	1.9 (1.6 to 2.4)	2.0 (1.3 to 2.9)
Pack-year of smoking (per one unit)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
Depression	2.1 (1.6 to 2.8)	1.8 (1.2 to 2.7)
Highest education		
Primary	1.3 (0.9 to 1.8)	1.1 (0.6 to 1.8)
Secondary	1 (ref)	1 (ref)
University	1.1 (0.9 to 1.3)	1.3 (1.0 to 1.9)
FEV ₁ /FVC<0.7	4.7 (3.3 to 6.9)	3.5 (1.5 to 8.3)
FVC (per 1 L)	0.9 (0.8 to 1.0)	0.7 (0.5 to 0.8)

Associations analysed using random effects logistic regression accounting for clustering by study centre. Unadjusted analyses were conducted for each factor separately. In the adjusted model, each factor was adjusted for all other factors in the model.
ref, reference.

and in offspring (RHINESSA). In parents, data were also available on breathlessness on the mMRC breathlessness scale.⁴

Data were obtained for both parents and offspring on age; sex; study centre; self-reported asthma diagnosed by a physician; history of

Table 3 Factors associated with breathlessness in offspring

Offspring factor	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 1 year)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
Female versus male	1.4 (1.1 to 1.7)	1.5 (1.1 to 2.0)
Body Mass Index (kg/m ²)		
<20	0.8 (0.5 to 1.2)	0.7 (0.4 to 1.1)
20–<25	1 (ref)	1 (ref)
25–<30	1.4 (1.0 to 1.8)	1.4 (1.0 to 1.9)
≥30	2.1 (1.5 to 2.9)	2.0 (1.3 to 3.1)
Asthma	7.7 (6.0 to 9.8)	7.4 (5.7 to 9.7)
Current smoking	2.1 (1.6 to 2.8)	2.1 (1.5 to 3.1)
Pack-year of smoking (per one unit)	1.1 (1.0 to 1.1)	1.1 (1.0 to 1.1)
Depression	3.2 (2.0 to 5.2)	–
Highest education		
Primary	1.8 (1.0 to 3.5)	1.2 (0.6 to 2.6)
Secondary	1 (ref)	1 (ref)
University	1.2 (0.9 to 1.5)	1.0 (0.8 to 1.4)

Associations analysed using random effects logistic regression accounting for clustering by study centre. Unadjusted analyses were conducted for each factor separately. In the adjusted model, each factor was adjusted for all other factors in the model. Due to high number of missing data, depression (n=1632 missing) and lung function (n=1381 missing) were not included in the multivariable model. When analysed in the subsample with data (in the fully adjusted model), depression associated with breathlessness (OR 2.2, 95% CI 1.2 to 3.9), whereas there were no clear associations for offspring airflow obstruction (FEV₁/FVC<0.7, p=0.18, or FVC, p=0.55).
ref, reference.

Table 4 Associations between breathlessness in parents and their offspring

Exposure variable	Association with offspring breathlessness, OR (95% CI)		
	Crude	Adjusted for parental factors only	Adjusted for both parental and offspring factors
Parental breathlessness, main analysis	1.7 (1.3 to 2.2) n=2476	1.8 (1.1 to 2.7) n=1143	1.8 (1.1 to 2.9) n=1040
Parental breathlessness, defined without concurrent wheeze	1.6 (1.1 to 2.5) n=2476	1.8 (0.9 to 3.4) n=1058	1.5 (0.7 to 3.2) n=961

Association between parental and offspring breathlessness, analysed using logistic regression, accounting for clustering within centres and between siblings. Estimates are expressed as ORs with 95% CIs. Adjustment factors in parents and offspring were age, sex, Body Mass Index category, asthma, current smoking, pack-years of smoking, depression (parents only), highest education, airflow limitation (FEV₁/FVC<0.7, parents only) and FVC (parents only). See table 1 for abbreviations.

depression; smoking status (never, former or current smoker); pack-years of smoking; level of highest completed education (primary, secondary, university); self-reported level of physical activity ('How frequently do you exercise?': almost every day; two to three times a week, once a week, less than once a week, or never). Assessments included height, weight and spirometry (FEV₁ and FVC). Postbronchodilator values were used if available or else prebronchodilator values. Predicted spirometry values were calculated using the Global Lung Function Initiative 2012 reference.²⁷

Statistical analyses

Characteristics of parents and offspring were summarised as frequencies and percentages for categorical variables, and as mean with SD or median with range or IQR for continuous variables with normal or skewed distributions, respectively.

Associations with breathlessness were analysed using multi-level logistic regression with random intercepts (using the STATA command 'meqrlogit'). All models accounted for clustering within study centres and between siblings. Associations were presented as OR with 95% CI. Associations between covariates and breathlessness were first analysed separately for parents and offspring. The main analysis was of the association between breathlessness in parents (exposure of main interest) and breathlessness in their offspring (outcome), adjusted for potential confounders on two levels (parents and offspring).

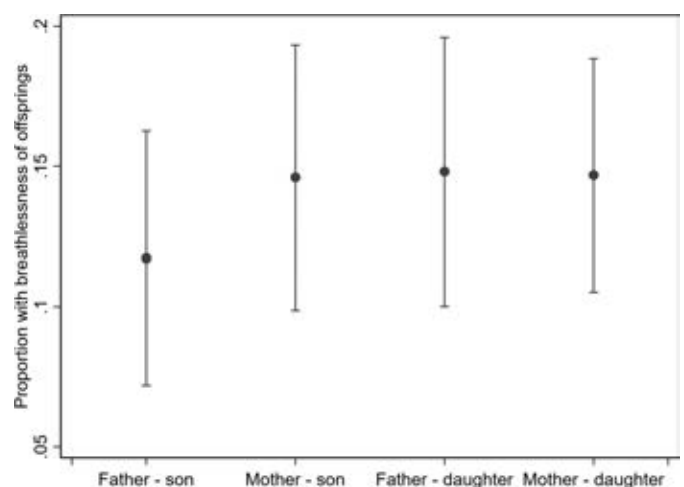


Figure 1 Breathlessness prevalence in offspring by sex of parent and child, adjusted for age of both generations. Analysed using random effects logistic regression accounting for clustering between siblings and within study centres. The model is fully adjusted for parental factors in table 2.

Potential confounders were selected a priori based on subject matter knowledge and previous population studies^{1-3 11-13 28} using a directed acyclical graph (shown in online supplemental figure S1).²⁹ Factors included were parental age, sex, Body Mass Index (BMI), asthma, current smoking, pack years of smoking, depression, education level, airflow obstruction ($FEV_1/FVC < 0.70$) and FVC. The primary model adjusted for factors measured in the parents, as these exposures preceded the outcome (offspring breathlessness). Models adjusted also for the similar factors in offspring were also fitted. We evaluated whether the association between parental and offspring breathlessness was modified by the sex of the parent and/or offspring by adding interaction terms to the fully adjusted model.

Sensitivity analyses were conducted: (1) adjusting for level of physical exercise in parents and offspring in addition to the other factors in the model. Physical activity was not included in the main model as it could be both a potential mediator or consequence (collider factor) rather than a determinant of breathlessness and thus potentially bias the findings; (2) not using the criterion 'breathlessness when having wheezing and whistling in the chest at any time in the last 12 months in the outcome definition of breathlessness, due to its potential relationship to asthma; and (3) also adjusting for offspring lung function (level of airflow limitation (FEV_1/FVC) and FVC) in the subcohort with data available; (4) analysing the association for parental breathlessness measured using the mMRC scale (available in parents only).⁴

Statistical significance was defined as a two-tailed *p* value of < 0.05 . All the analyses were conducted using STATA V.16.0.

RESULTS

A total of 1720 parents (mean age at inclusion 36 years (SD 6.4), 55% mothers) and 2476 offspring (mean age 30 years (SD 7.7), 55% daughters) were included in the analysis (table 1). Breathlessness was reported by 809 (32.7%) of parents and by 363 (14.7%) of offspring. Characteristics of participants by the presence of offspring breathlessness are shown in table 1.

Asthma was strongly related to breathlessness, both among parents and offspring (table 1). Asthma was more common in people with breathlessness versus those without breathlessness, both in parents (36.7% vs 4.5%, $p < 0.001$) and in the offspring (54.6% vs 13.5%, $p < 0.001$). Thus, about half of offspring with breathlessness also reported having asthma.

In parents, factors independently associated with higher breathlessness prevalence were male sex, obesity, asthma (strong association with adjusted OR 16.3, 95% CI 10.1 to 26.1), current smoking, history of depression, presence of airflow obstruction and lower FVC (table 2).

In offspring, a similar pattern of associations was found as that in parents (table 3), except that the sex distribution was reversed with greater breathlessness in women. Asthma was the factor most strongly related to breathlessness also in the offspring (OR 7.4, 95% CI 5.7 to 9.7). In these two samples of relatively young adults, age was not associated with breathlessness, neither in parents nor offspring.

In the two-generation analyses shown in table 4, parents with breathlessness were more likely to have offspring with breathlessness (19.5% vs 12.3% of their offspring reporting breathlessness, $p < 0.001$; crude OR 1.7, 95% CI 1.3 to 2.2). In multivariable analysis, parents with breathlessness had independently increased risks of offspring reporting breathlessness. The association remained unchanged even after adjusting for both parental and offspring factors including asthma (adjusted OR 1.8, 95% CI 1.1 to 2.9) (table 4). In the sensitivity analysis excluding breathlessness in relation to wheeze from the outcome definition (as this was most likely related to asthma), the association between parental and offspring breathlessness was somewhat weaker (OR 1.5, 95% CI 0.7 to 3.2), and the precision decreased (and fewer participants and outcome events were included in the analyses) as shown by the wider CI in table 4. When also adjusting for offspring lung function ($n = 1381$ (56%) with data) in addition to the other

parental and offspring factors, parental breathlessness was still strongly associated with increased breathlessness in offspring (adjusted OR 2.4, 95% CI 1.1 to 5.3).

The association between parental breathlessness and higher risk of breathlessness in offspring was consistent when defining parental breathlessness using the mMRC scale. Compared with those with mMRC=0, parents with a mMRC of ≥ 2 had a more than three times increased odds of having offspring with breathlessness (OR 3.2, 95% CI 1.4 to 7.5), adjusting for both parental and offspring factors.

Female sex of either the parent (mother with breathlessness) or offspring (daughter) was associated with slightly higher prevalence of offspring breathlessness, as shown in figure 1. However, the sex of parent or offspring did not modify the association between parental and offspring breathlessness (*p* for interaction=0.48 by likelihood ratio test). The association between parental and offspring breathlessness was similar when adjusting also for physical exercise of parents and offspring in addition to the other factors in the model (OR 1.8, 95% CI 1.1 to 3.0).

DISCUSSION

In this large international study of 1720 parents and 2476 offspring, there was substantial clustering of breathlessness across two generations. Parents who reported breathlessness as young adults were more likely to have offspring who had developed breathlessness as young adults. Obesity, smoking, depression, asthma, lower lung function and female sex were associated with breathlessness in each generation. If the parents had breathlessness, the odds of having an offspring with breathlessness was increased by 80%, even after controlling for these determinants of breathlessness in both the parents and the offspring.

This is the first study exploring breathlessness across generations. The findings extend the understanding of breathlessness in several important ways. First, it finds that factors associated with breathlessness were similar in both parents and their offspring, which is a novel finding. The expected associations with increased breathlessness were seen for factors such as obesity, airflow obstruction and FVC, which supports the validity of the present findings. In a novel second step, we reported a strong association between parental and offspring breathlessness. Third, this clustering of breathlessness across the generations was not explained by a range of the known risk factors for breathlessness in the population.^{1-3 11-13 28} Finally, this association did not show clear sex-specific patterns, although a weaker association was indicated for the father-son relationships.

Heredity of breathlessness, a multifactorial and multidimensional symptom,¹⁰ likely involves a complex interplay of social, behavioural and other environmental, as well as genetic and possibly epigenetic factors. Genetic factors have been implicated in the development of airflow limitation, reduced lung function and impaired ventilatory capacity,²¹ which are important determinants of breathlessness.¹³⁻¹⁵ Lung function and respiratory symptoms could also be influenced by early life and environmental exposures.^{9 22} Genetic factors predict increased risk of developing chronic airflow limitation, independent of smoking status,²¹ and influence the clinical phenotype and functional impairment in COPD.³⁰ Other partly inheritable factors include BMI and body fat distribution,³¹ and level of physical activity and sedentary behaviour.²³

Genetic heritability has also been shown for anxiety and panic, including increased anxiety response to hypercapnia in a twin study.³² Mood including anxiety and depression is strongly related to breathlessness perception, and clustering of breathlessness across generations might be influenced by inheritable personality traits.³³ In a study of pain, the symptom phenotype had significant and positive genetic correlations with depressive symptoms, major depressive disorders and neuroticism, and all pain phenotypes were heritable.³⁴ Similar genetic studies of breathlessness are lacking.

Asthma is a likely heritable cause of breathlessness across generations, especially in younger people who have a relatively

high prevalence of asthma compared with that of other chronic conditions causing breathlessness.¹⁶ Asthma has substantial genetic components,¹⁸ as demonstrated in twin studies.¹⁹ The cross-generational association in the present study became somewhat weaker when excluding concurrent wheeze in the breathlessness definition, indicating that (undiagnosed) asthma could be a factor underpinning the present heredity pattern for breathlessness. Heritability was supported as the association remained in the most fully adjusted model which accounted also for lung function of both generations.

Strengths of this study include the use of a large, well characterised, multicentre database. The analysis accounted for clustering within centres and among siblings and evaluated a range of relevant factors in parents and their offspring.

A limitation was the definition of breathlessness. Optimally, breathlessness should be measured using validated instruments at standardised level of physical activity,³⁵ but such measurements are rarely available in epidemiological and large-scale studies or across generations. We used available data on breathlessness, using a similar definition in parents and offspring. Findings were similar when analysing breathlessness using mMRC (available in parents only) and in a sensitivity analysis excluding concurrent wheeze. The breathlessness questions used may relate to varying extent to asthma, and the persistent strong association after adjusting for covariates including a history of asthma might reflect undiagnosed disease.

Although the analyses controlled for a range of relevant clinical factors including lung function, data were unavailable on a number of potential determinants of breathlessness including heart function and physical fitness, which should be further explored across generations. Another potential limitation is that many invited parents and offspring did not participate in the study. A previous analysis of the influence of missing data in the Respiratory Health in Northern Europe study showed that participants tended to be healthier, but that exposure–outcome associations remained unchanged by this selection.³⁶ Based on this, while the prevalence of factors may be underestimated (including breathlessness), the analysis estimates are likely to be valid.

We propose further research to validate of the present findings using standardised measurement of multidimensional breathlessness; evaluate the influence of anxiety, psychosocial factors including personality traits, and genetic as well as epigenetic variations. This research is important for improved knowledge on the mechanisms underpinning breathlessness across the generations, to identify risk groups for developing severe breathlessness and to identify environmental factors amenable to interventions to improve respiratory health of coming generations.

In conclusion, people with breathlessness were more likely to have children who reported breathlessness as young adults. The clustering of breathlessness across generations was independent of lung function, asthma and a range of potential confounders in both generations and warrants further investigation.

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Ethics approval Written informed consent was obtained from each participant and the study was approved by the medical research ethics committee for each study centre according to national legislation (listen in the online supplemental file).

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REFERENCES

1. Lopez Varela MV, Montes de Oca M, Halbert RJ, et al. Sex-Related differences in COPD in five Latin American cities: the PLATINO study. *Eur Respir J* 2010;36:1034–41.
2. Grönseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnoea prevalence: results from the BOLD study. *Eur Respir J* 2014;43:1610–20.
3. Bowden JA, To THM, Abernethy AP, et al. Predictors of chronic breathlessness: a large population study. *BMC Public Health* 2011;11:33.
4. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–6.
5. Jones PW, Adamek L, Nadeau G, et al. Comparisons of health status scores with MRC grades in COPD: implications for the gold 2011 classification. *Eur Respir J* 2013;42:647–54.
6. Currow DC, Dal Grande E, Ferreira D, et al. Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. *Thorax* 2017;72:1151–3.
7. Figarska SM, Boezen HM, Vonk JM. Dyspnea severity, changes in dyspnea status and mortality in the general population: the Vloetwede/Vlaardingen study. *Eur J Epidemiol* 2012;27:867–76.
8. Nishimura K, Izumi T, Tsukino M, et al. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;121:1434–40.
9. Svanes C, Sunyer J, Plana E, et al. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;65:14–20.
10. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012;185:435–52.
11. Currow DC, Dal Grande E, Sidhu C, et al. The independent association of overweight and obesity with breathlessness in adults: a cross-sectional, population-based study. *Eur Respir J* 2017;50:1700558. doi:10.1183/13993003.00558-2017
12. Sandberg J, Ekström M, Börjesson M, et al. Underlying contributing conditions to breathlessness among middle-aged individuals in the general population: a cross-sectional study. *BMJ Open Respir Res* 2020;7:e000643.
13. Ekström M, Schiöler L, Grönseth R, et al. Absolute values of lung function explain the sex difference in breathlessness in the general population. *Eur Respir J* 2017;49:1602047.
14. Ekström M, Sundh J, Schiöler L, et al. Absolute lung size and the sex difference in breathlessness in the general population. *PLoS One* 2018;13:e0190876.
15. Ekström M, Bornefalk-Hermansson A, Wysham N, et al. Spirometric volumes and breathlessness across levels of airflow limitation: the COPDGen study. *Am J Respir Crit Care Med* 2018;198:678–81.
16. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. *Front Pediatr* 2019;7:246.
17. Thomsen SF. Genetics of asthma: an introduction for the clinician. *Eur Clin Respir J* 2015;2:24643.
18. Johansson AS, Rask-Andersen M, Karlsson T, et al. Genome-wide association analysis of 350 000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema. *Hum Mol Genet* 2019;28:4022–41.
19. Ullemar V, Magnusson PKE, Lundholm C, et al. Heritability and confirmation of genetic association studies for childhood asthma in twins. *Allergy* 2016;71:230–8.
20. Soler Artigas M, Loth DW, Wain LV, et al. Genome-Wide association and large-scale follow up identifies 16 new loci influencing lung function. *Nat Genet* 2011;43:1082–90.
21. Shrine N, Guyatt AL, Erzurumluoglu AM, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. *Nat Genet* 2019;51:481–93.
22. Li LSK, Williams MT, Johnston KN, et al. Parental and life-course influences on symptomatic airflow obstruction. *ERJ Open Res* 2020;6:00343–2019.
23. Leite JMRS, Soler JMP, Horimoto ARVR, et al. Heritability and sex-specific genetic effects of self-reported physical activity in a Brazilian highly admixed population. *Hum Hered* 2019;84:151–8.
24. Svanes C, Koppin J, Skulstad SM, et al. Father's environment before conception and asthma risk in his children: a multi-generation analysis of the respiratory health in northern Europe study. *Int J Epidemiol* 2017;46:235–45.
25. von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806.
26. Kuiper IN, Svanes C, Benediktsdottir B, et al. Agreement in reporting of asthma by parents or offspring - the RHINESSA generation study. *BMC Pulm Med* 2018;18:122.
27. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-Ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
28. Ekström M, Schiöler L, Grönseth R, et al. Absolute values of lung function explain the sex difference in breathlessness in the general population. *Eur Respir J* 2017;49:1602047.
29. Textor J, Hardt J, Knüppel S, DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology* 2011;22:745.
30. Hersh CP, Demeo DL, Lazarus R, et al. Genetic association analysis of functional impairment in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:977–84.
31. Rask-Andersen M, Karlsson T, Ek WE, et al. Genome-Wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. *Nat Commun* 2019;10:339.
32. Battaglia M, Pesenti-Griffi P, Spatola CAM, et al. A twin study of the common vulnerability between heightened sensitivity to hypercapnia and panic disorder. *Am J Med Genet B Neuropsychiatr Genet* 2008;147B:586–93.
33. Hou B, Ji L, Chen Z, et al. Role of rs454214 in personality mediated depression and subjective well-being. *Sci Rep* 2020;10:5702.
34. Meng W, Adams MJ, Reel P, et al. Genetic correlations between pain phenotypes and depression and neuroticism. *Eur J Hum Genet* 2020;28:358–66.
35. Ekström M, Elmhög V, Lindow T, et al. Breathlessness measurement should be standardised for the level of exertion. *Eur Respir J* 2018;51:1800486.
36. Johannessen A, Verlaato G, Benediktsdottir B, et al. Longterm follow-up in European respiratory health studies - patterns and implications. *BMC Pulm Med* 2014;14:63.

Pandemia de COVID-19: desigualdades de saúde em crianças e jovens

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INTRODUÇÃO

A pandemia da COVID-19 é uma crise de direitos da criança que desafia a sobrevivência e o desenvolvimento a longo prazo de crianças e jovens em todo o mundo. As consequências pandêmicas e indiretas das medidas de saúde pública associadas estão a agravar os fatores de stresse pré-existentes à sobrevivência com que as famílias marginalizadas se confrontam todos os dias, com consequências prejudiciais e desproporcionais. A interrupção dos serviços, a redução do acesso aos cuidados de saúde, a interrupção da educação e da escolaridade infantil e o declínio económico a longo prazo serão mais prejudiciais para as crianças do que o próprio vírus. A Sociedade Internacional de Pediatria Social e Saúde Infantil (ISSOP) é uma organização global de profissionais de saúde que visa melhorar a saúde e o bem-estar das crianças e dos jovens centrada na criança, na doença e na saúde, no contexto da sua sociedade, ambiente, escola e família. Esta Declaração de Posição da ISSOP descreve o impacto da COVID-19 nas desigualdades na saúde infantil e juvenil e apela à ação dos governos, profissionais de saúde, investigadores e organizações ativistas.

DECLARAÇÃO DO PROBLEMA

A pandemia da COVID-19 irá ampliar a desigualdade, a menos que atuem para garantir o contrário

As melhorias na saúde e no bem-estar de crianças e jovens nos últimos 20 anos, em parte impulsionadas pelos Objetivos de Desenvolvimento Sustentável e do Milénio, correm o risco de ser revertidas, com desigualdades crescentes dentro de cada país e entre países.¹ Nos países de rendimentos baixos e médios (PRBM), a pandemia impõe um fardo adicional a sistemas financeiros e de saúde frágeis e com limitações de recursos pré-existent.^{2,3} A curto prazo, a interrupção do acesso à saúde, educação e serviços sociais agrava os resultados de saúde em crianças e jovens desfavorecidos.³ Contudo, os impactos a longo prazo na saúde, bem-estar, alfabetização, rendimentos, oportunidades profissionais,

habitação e efeitos intergeracionais são potencialmente devastadores⁴ (figura 1).

Uma abordagem baseada nos direitos da criança para definir o impacto da pandemia da COVID-19 nas crianças

Os direitos enunciados na Convenção das Nações Unidas sobre os Direitos da Criança, adotada por todos os países, exceto os EUA, têm sido difíceis de fazer valer durante a pandemia.

Direito à saúde e ao acesso aos cuidados de saúde (Artigo 24)

- ▶ As interrupções de vários sistemas devido a confinamentos, restrições de viagem e medo diminuem o acesso a cuidados pré-natais, programas de desenvolvimento na primeira infância e serviços básicos de saúde e humanos.⁴
- ▶ Os nascimentos em hospitais diminuíram em 21% na Índia e em alguns países africanos. A separação pós-parto diminuiu as taxas de amamentação em muitas partes do mundo.²
- ▶ As visitas às instalações de cuidados de saúde diminuíram e os programas de imunização foram suspensos globalmente, com uma redução de 69% na Índia na vacinação contra sarampo, papera e rubéola.¹ Os casos de poliomielite selvagem nova e derivada da vacinação que surgiram antes da pandemia aumentaram este ano.²
- ▶ A interrupção das cadeias de abastecimento e o custo tem restringido a aquisição de sabão, desinfetante de mãos, testes de diagnóstico, medicamentos, máscaras faciais e outro equipamento de proteção pessoal (PPE), ao mesmo tempo que os países têm visto o patrocínio de remédios químicos ou à base de plantas não comprovados.²

Direito à educação (Artigo 28)

A perturbação na educação e no apoio escolar tem potencial para impactos permanentes na capacidade humana em todos os contextos. Os encerramentos de escolas cortam as ligações precárias à educação e aos apoios sociais de base escolar, reduzindo as oportunidades de educação e emprego e potencialmente levando ao envolvimento com a justiça juvenil e ao desemprego.⁴ Os encerramentos de escolas têm maior impacto nas crianças com deficiências e dificuldades de aprendizagem e, nos PRBM, com acesso reduzido ao ensino online.³

Direito a viver livre de exploração: trabalho infantil, abuso de drogas, exploração sexual, rapto, recrutamento, tráfico ou qualquer atividade que possa prejudicar o bem-estar ou o desenvolvimento (Artigos 32/34/35/36).

Proteção contra a violência, o abuso ou a negligência (Artigo 19)

A perda de acesso à escola e às oportunidades recreativas construtivas e o encerramento das instalações infantis reduziram a proteção das crianças e aumentaram o risco de abuso infantil, de trabalho não regulamentado e de recrutamento de combatentes entre rapazes adolescentes em PRBM.^{1,5} As dificuldades financeiras, a redução da observação extrafamiliar e a sobrecarga dos serviços de proteção infantil a nível global resultaram num aumento da violência doméstica e da violência sexual e baseada no género, estando as raparigas em maior risco de exploração e abuso sexuais, aumento do casamento infantil e menor probabilidade de regressarem à escola, o que aumenta ainda mais as disparidades de género.^{1,5}

O interesse superior da criança é uma consideração primordial (Artigo 3).

Direito a uma sobrevivência e desenvolvimento ótimos (Artigo 6).

Direito a um nível de vida adequado que apoie as necessidades mentais e físicas (Artigo 27).

Esperam-se impactos diferenciados nas crianças e jovens que vivem na pobreza devido a uma maior dependência da economia informal, a menores reservas financeiras, a

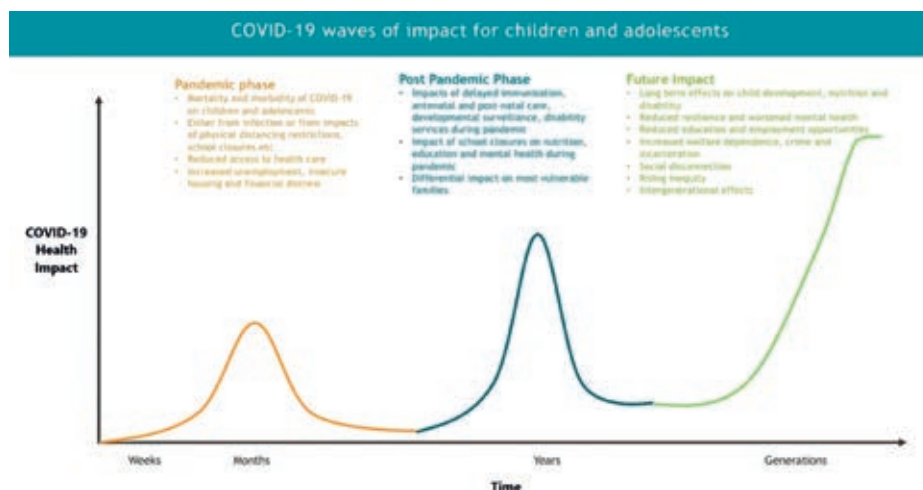


Figura 1 Ondas de impacto do COVID-19 para crianças e adolescentes.

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um acesso reduzido a soluções tecnológicas para os cuidados de saúde e educação e a elevados níveis de sofrimento psicológico.¹ As comunidades sobrepovoadas em PRBM sem água canalizada são incapazes de aderir aos regulamentos relativos ao distanciamento físico ou à lavagem das mãos.² A fome tem sido exacerbada pela redução do rendimento dos cuidadores e pelo encerramento dos programas de alimentação escolar, das sopas comunitárias e da distribuição de alimentos governamentais.¹ Em países de rendimentos elevados (PRE), as crianças em agregados familiares de baixos rendimentos e pertencentes a minorias étnicas correm um risco acrescido de morte de adultos, deixando os agregados familiares sem um ou mais cuidadores.³

Existem oportunidades para usar a pandemia na redução das desigualdades, aproveitar os aspetos positivos e construir um futuro sustentável?

A redução da pobreza infantil, abordando os determinantes da saúde e reforçando os sistemas de saúde para assegurar a cobertura universal da saúde fará avançar os direitos das crianças e dos jovens e melhorará a saúde e o bem-estar globais.^{1,3} Soluções inovadoras de saúde e bem-estar que surgiram durante a pandemia podem ajudar a acelerar este ideal.

- Em Kerala, na Índia, redes de grupos de mulheres criaram PPE, estabeleceram cozinhas comunitárias e proporcionaram intervenções educativas, de lazer e de aconselhamento para crianças.
- No Senegal, foram desenvolvidos testes de diagnóstico baratos; no Gana e no Quênia, foram criados fornecimentos locais de máscaras.
- Na Somália, os assistentes sociais estudantis aumentaram a segurança das crianças no contexto de escassez de mão-de-obra. Em contextos PRE, o aumento das competências de tele saúde está a criar uma prestação de cuidados de saúde mais acessível em áreas remotas e inacessíveis.

Muitos países expandiram o alcance dos pacotes de rede de segurança social, sem abrigo, financeiros e de apoio ao emprego.⁴ Foram implementadas medidas para mitigar a instabilidade habitacional, o peso do pagamento de rendas e hipotecas e os despejos.¹ De particular importância global, a pandemia causou uma redução nas emissões de carbono e uma melhor qualidade do ar. Do mesmo modo, a Rede das Nações Unidas para as Migrações recomendou às nações a imposição de uma moratória à detenção de imigrantes.

Recomendações de ação

A ISSOP reconhece os desafios durante a pandemia, mas, no entanto, exorta os gover-

nos, prestadores de serviços de saúde infantil, investigadores e organizações ativistas a responderem de forma urgente e definitiva através de uma resposta baseada nos direitos da criança.

Governos

- Direcionar recursos para o cuidado e proteção de crianças e jovens.⁴
- Prevenir a escassez de alimentos e a fome; apoiar a produção local de alimentos.^{2,3}
- Apoiar a educação na primeira infância.⁵
- Assegurar o acesso aos serviços de saúde, educação e bem-estar.^{1,3}
- Fornecer acesso a habitação, água e saneamento.¹
- Controlar o trabalho infantil não regulamentado, o abuso de crianças e o casamento precoce. Investir em infraestruturas e mão-de-obra sociais na educação, saúde e cuidados sociais para crianças e jovens vulneráveis.³
- Combinar respostas de emergência de proteção social com transições para programas permanentes.¹
- Expandir e proteger o emprego.^{1,3}
- Estabelecer programas de apoio financeiro, salário mínimo básico universal ou outras estratégias para apoiar as famílias.³
- Assegurar que os grupos marginalizados, incluindo os requerentes de asilo, tenham acesso equitativo a serviços e benefícios.¹

Pediatras e prestadores de cuidados de saúde infantil

- Preservar e melhorar os serviços de saúde maternos, infantis e juvenis de rotina, tendo a equidade como um objetivo específico.^{1,2}
- Afirmar a dignidade e os direitos das crianças e dos jovens.³
- Defender o acesso a cuidados de saúde, serviços de proteção, habitação, assistência social e políticas de emprego que apoiem as crianças e as famílias.³
- Promover serviços de saúde mental acessíveis e de resiliência para as famílias.^{3,5}
- Desenvolver a tele saúde e tecnologias que sejam sustentáveis e adaptadas ao ambiente específico.³
- Manter o foco na criança e prestar serviços essenciais presenciais sempre que necessário.³

Investigadores e grupos ativistas

- Promoção dos direitos da criança, da justiça social e da equidade na saúde.^{1,5}
- Colaborar com parceiros fundamentais em todo o mundo para descobrir e divulgar evidências destinadas a mitigar os impactos pandémicos nas crianças e jovens.³
- Assegurar que as crianças e jovens em PRBM beneficiem dos achados da in-

vestigação, da imunização e das opções de tratamento para a COVID-19.

- Mobilizar as sociedades profissionais internacionais e colaborar com a sociedade civil, especialmente crianças e jovens, em todos os aspetos da pandemia.³

CONCLUSÃO

As mortes devidas à COVID-19 serão uma pequena proporção das futuras mortes de crianças a nível global. A maioria das mortes irá resultar indiretamente do fraco acesso a nutrição, habitação, água e saneamento, vacinas e cuidados de saúde universais. Esta declaração da ISSOP oferece ações claras para assegurar que a pandemia não agrave as desigualdades existentes na saúde com consequências duradouras e intergeracionais para crianças e jovens. Esta pandemia não deve impedir o frágil progresso alcançado ao longo de décadas na saúde e bem-estar de crianças e jovens, mas deve atuar como catalisador para um mundo mais justo e equitativo.

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REFERENCES

1. Loperfido L, Burgess M. The hidden impact of COVID-19 on child poverty. London: Save the Children International, 2020.
2. Cash R, Patel V. Has COVID-19 subverted global health? *Lancet* 2020;395:1687–8.
3. International Society of Social Pediatrics and Child Health. Advancing health equity and social justice in response to COVID-19, 2020. Available: https://www.issop.org/cmdownloads/issop_covid-declaration/
4. Tirivayi N, Richardson D, Gavrilovic M. A rapid review of economic policy and social protection responses to health and economic crises and their effects on children – lessons for the COVID-19 pandemic response. Florence: UNICEF Office of Research – Innocenti, 2020.
5. United Nations Children's Fund (UNICEF). Protecting children from violence in the time of COVID-19: disruptions in prevention and response services. New York: UNICEF, 2020.

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