

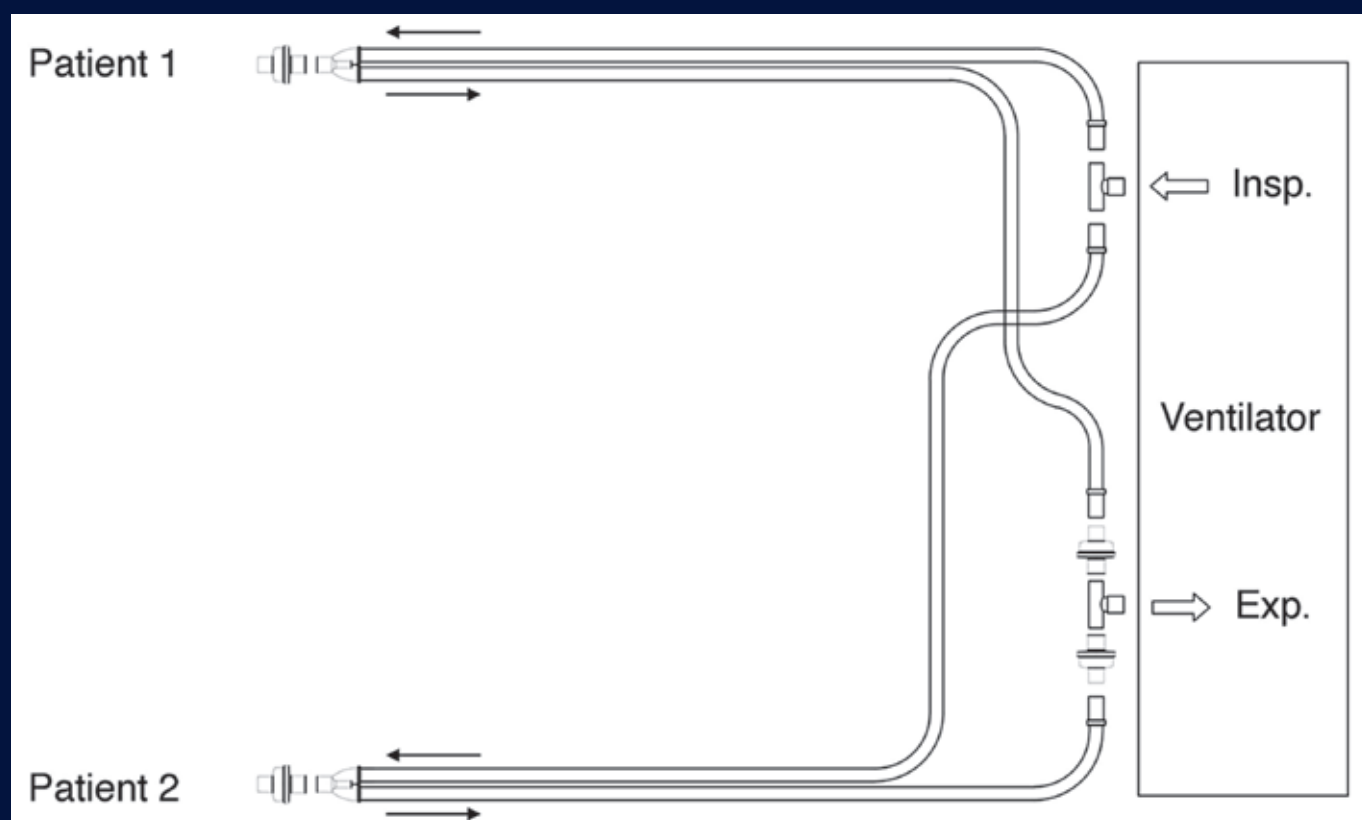
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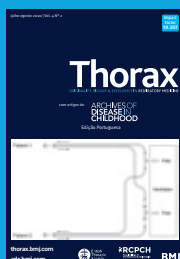


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Editorial

Neste número, os artigos seleccionados das Revistas *Thorax* e *Archives of Disease in Childhood* sublinham algumas das tendências atuais de investigação e orientação clínica com evidência para os fatores com influências determinantes em saúde:

- Prevenir e lidar com as doenças transmissíveis, como na situação pandémica causada pelo SARS-CoV-2, sem esquecer os programas de rastreio, prevenção através do Programas de Imunização, especialmente na criança e o impacto da legislação;
- Valorizar exposições ambientais nocivas com impacto na prevalência das doenças não transmissíveis, como é o caso da exposição ao fumo do tabaco e da DPOC;
- Identificar fatores de risco associados a doenças crónicas, como no artigo que descreve a associação entre a apneia obstrutiva em idade pediátrica e valores de tensão arterial mais elevado a longo prazo;
- Responder a questões de variabilidade clínica através da identificação cada vez mais sofisticada de fatores biológicos, como no caso da valorização da microbiota nas agudizações da DPOC – um estado da arte;

E, *last but not least*,

- Analisar indicadores de sucesso ou insucesso de *outcomes* com impacto na qualidade de serviços e prognóstico como avaliado no artigo “A admissão hospitalar no Reino Unido durante o fim-de-semana não influencia o prognóstico de adultos com pneumonia adquirida na comunidade”.

Aqui e ali, uma referência crescente à telemedicina, neste número com os resultados de um ensaio clínico que compara a telerreabilitação pulmonar com a reabilitação pulmonar tradicional, abrindo janelas para a evolução dos cuidados de saúde mantendo a personalização, mas insistindo no conforto e na sustentabilidade. São inúmeras as razões para ler atentamente e com detalhe esta publicação.

Desejamos boas leituras, mesmo em tempo de férias e de um intervalo merecido no ano árduo que vivemos...

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A apneia obstrutiva do sono na criança é um fator de risco independente de hipertensão na idade adulta?

Rosemary S C Horne,¹ Montida Veeravigrom²

Mais de um terço das crianças ressona enquanto dorme e, até à última década, este facto tem sido considerado benigno, tanto pelos pais como pelos profissionais de saúde. O ressonar era considerado como algo que iria desaparecer espontaneamente. O ressonar é o sintoma característico da perturbação respiratória do sono (DRS), que varia em termos de gravidade desde o simples ressonar ou ressonar primário até à apneia obstrutiva do sono (AOS) que atinge até 6% das crianças.¹ A incidência de picos de DRS nos anos pré-escolares, quando o tamanho das adenóides e amígdalas - a causa primária do ressonar infantil do DRS - atinge o pico em relação ao esqueleto ósseo. Adicionalmente, a obesidade infantil aumenta o risco de AOS, particularmente em crianças mais velhas. Nos adultos, a AOS é reconhecida como um fator de risco independente para hipertensão e não diminuição da pressão arterial noturna, ambos associados a doenças cardiovasculares, cerebrovasculares e doença renal em fase terminal.²

Estudos recentes em crianças demonstraram que a pressão arterial encontra-se elevada nas crianças do primeiro ciclo escolar com todos os graus de DRS, incluindo ressonar primário,³ e o início de pressão arterial elevada é evidente em crianças com AOS entre os 3-5 anos de idade.⁴ A obesidade compõe os efeitos adversos da AOS no sistema cardiovascular.⁵ O que tem faltado na literatura pediátrica é o conhecimento dos efeitos a longo prazo do DRS sobre a pressão arterial e se o DRS infantil é um fator determinante da pressão arterial adulta. O estudo de Chan *et al* abordou esta importante questão - acompanhando 243 crianças entre os 6 e os 13 anos de idade, recrutadas na comunidade durante um período de 10 anos, até à adolescência e à idade adulta. O estudo utilizou o padrão de referência da polissonografia para determinar a gra-

vidade do DRS, em conjunto com a monitorização ambulatoria da tensão arterial durante 24 horas em ambos os intervalos de tempo.

O estudo concluiu que as crianças com AOS moderada a grave no início do estudo apresentaram pressão arterial sistólica mais elevada (média 6,5 mmHg) e uma redução da diminuição de pressão arterial noturna (média 4%), quando ajustada para idade, sexo, índice de massa corporal (IMC) e altura no início do estudo, e a presença de AOS no seguimento. Globalmente, o estudo constatou que as crianças do primeiro ciclo escolar com AOS moderada a grave apresentavam um risco 2,5 vezes superior de hipertensão e um risco 1,3 vezes superior de redução de diminuição de PA noturna. Estes resultados sugerem que existe um efeito limiar entre a AOS infantil e a pressão arterial adulta, uma vez que apenas a AOS moderada a grave esteve associada a resultados cardiovasculares adversos. Existem atualmente evidências de que qualquer melhoria na gravidade da AOS diminui a pressão arterial, o que se acentua em crianças com um IMC mais elevado.^{6,7}

O estudo de Chan *et al* observou que muitos pais estavam relutantes em que o seu filho fosse submetido a qualquer tratamento pois consideravam que o seu filho seria assintomático. Apenas 20% das crianças com AOS receberam tratamento cirúrgico e 14% receberam tratamento médico. Um segundo artigo sobre a mesma coorte de crianças relatou que 30% das crianças com AOS resolveram espontaneamente a doença (índice de apneia-hipopneia obstrutiva <1 evento/h).⁸ Os 22% que continuaram a apresentar AOS eram predominantemente do sexo masculino e apresentavam um *z-score* de IMC mais elevado no início do estudo. Adicionalmente, o estudo demonstrou que a AOS mais grave em crianças com mais de 10 anos tendia a persistir, enquanto que a AOS diagnosticada em crianças mais novas apresentava menos probabilidades de se correlacionar com a sua persistência.

O estudo salienta a necessidade urgente de rastrear e tratar todas as crian-

ças para o DBS o mais breve possível e, sobretudo, que as crianças mais velhas e as crianças com excesso de peso ou obesas requerem particular atenção e acompanhamento para reduzir as hipóteses de continuarem a sofrer de AOS na idade adulta e, por sua vez, de aumentarem o risco de hipertensão, doenças cardiovasculares, cerebrovasculares e doença renal em fase terminal.

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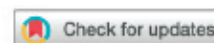
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Dar prioridade à vigilância pediátrica durante a pandemia de COVID-19

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Children may represent only a small proportion of confirmed cases of coronavirus disease 2019 (COVID-19) in the current pandemic, but they are at the centre of every paediatrician's mind and the primary focus of their work. While much of the COVID-19 pandemic preparedness and response is rightly focused on adults, paediatricians should be reassured that children have not been forgotten. In the UK, the Royal College of Paediatrics and Child Health (RCPC) has produced extensive guidance for paediatricians that are available online (<https://www.rcpch.ac.uk/resources/covid-19-guidance-paediatric-services>). At the same time, Public Health England (PHE) provides regularly updated guidance for healthcare professionals, focusing particularly on infection control and testing for COVID-19 (<https://www.gov.uk/government/collections/wuhan-novel-coronavirus>). PHE is also working with National Health Service (NHS) and academic colleagues to answer important questions about childhood COVID-19, including the course of illness and outcomes in neonates and children, the risk of vertical transmission during pregnancy and the role of children in infection and disease transmission in the community.

GLOBAL COVID-19 SITUATION

Coronaviruses typically cause mild upper respiratory tract infections, but they have been responsible for three major outbreaks associated with severe illness and death: severe acute respiratory syndrome (SARS) in 2002, Middle East respiratory syndrome (MERS) in 2012 and, now, COVID-19.

Genomic analyses indicate that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, originated in bats¹ and was probably

transmitted to humans through an intermediate host, most likely pangolins (scaly anteater-like mammals).² The illness was first recognised in Wuhan, Hubei Province, China, in early December 2019, and spread rapidly across the continents, leading the World Health Organization (WHO) to declare COVID-19 a public health emergency of international concern (PHEIC) on 30 January 2020 and then a global pandemic on 12 March 2020. By 28 April 2020, there were >3.2 million COVID-19 cases and >225 000 deaths worldwide (<https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncovcases>).

COVID-19 IN THE UK

In the UK, imported COVID-19 cases were first diagnosed at the end of January 2020 and increased slowly because of the initial containment procedures involving rapid identification and isolation of symptomatic cases, with extensive contact tracing (<https://www.gov.uk/guidance/high-consequence-infectious-diseaseshcd>). On 4 March, there were only 85 cases but these increased rapidly to 456 on 11 March, 2626 on 18 March, 17089 on 28 March, 25150 on 31 March, 108692 cases on 17 April and 161 145 cases with 21 678 deaths on 28 April 2020 (<https://www.gov.uk/guidance/coronavirus-covid-19-information-for-the-public>).

COVID-19 IN CHILDREN

In China, children under the age of 10 years (416 cases, no deaths) and

10–19 years (549 cases, one death) each represented <1% of the total number of 72314 confirmed and suspected COVID-19 cases until 11 February,³ a similar proportion to the SARS and MERS outbreaks.^{4,5} In another case series of 2143 children with COVID-19, 94% of children had asymptomatic, mild or moderate disease (table 1).⁶ Children were much less likely to develop severe or critical disease (5.9%) than adults (18.5%). Infants aged <1 year had the highest proportion with severe or critical cases (11%), which declined to 4% in individuals aged 11–15 years; only one teenager in this cohort died.⁶ Overall, there have been very few deaths due to COVID-19 in individuals aged <50 years but case fatality rates increase exponentially after this age, reaching 15% among >80 years.³

Data on childhood COVID-19 from other countries are slowly emerging. In the US, between 12 February and 02 April 2020, children aged <18 years accounted for 1.7% (2572/149 082) of cases where age was reported; 20% were hospitalised, 23% had ≥1 comorbidity and three died.⁷ The main comorbidities were chronic lung disease including asthma, cardiovascular disease and immunosuppression; such children were more likely to be hospitalised and admitted to intensive care units.⁷

Many questions, however, remain unanswered. It is still not clear why children have a lower risk of COVID-19 and develop milder disease. The answer is likely to be related to both exposure and host factors. Unlike most other infectious diseases, children primarily acquire SARS-CoV-2 from adults, usually a family member; this mode of transmission may be less efficient and result in a lower infecting dose. Alternatively, the maturity, function and/or avidity of the human receptor for SARS-CoV-2, the

Table 1 Critérios de diagnóstico utilizados numa grande série pediátrica de 2143 casos de COVID-19 infantil na China⁶

Gravidade da doença	Descrição da doença
1. Assintomática	PCR positiva a nariz/garganta para SARS-CoV-2 em criança sem sintomas ou sinais clínicos e com imagem torácica normal, se realizada.
2. Ligeira	Sintomas de infeção aguda das vias respiratórias superiores, incluindo febre, fadiga, mialgia, tosse, dor de garganta, corrimento nasal e espirros. O exame físico revela congestão da faringe mas sem anomalias na auscultação. Alguns casos podem apresentar-se sem febre ou apenas com sintomas gastrointestinais, tais como náuseas, vômitos, dores abdominais e diarreia.
3. Moderada	Apresentação com pneumonia, febre e tosse (inicialmente seca e depois produtiva), alguns doentes podem apresentar pleira ou sons respiratórios transmitidos, mas sem hipoxemia óbvia, p. ex. falta de ar. Alguns casos podem não apresentar sintomas ou sinais clínicos, mas a TC ao tórax apresenta lesões pulmonares, que são subclínicas.
4. Grave	Sintomas respiratórios precoces, como febre e tosse, podem ser acompanhados por sintomas gastrointestinais, como diarreia. A doença progride normalmente durante cerca de 1 semana e ocorre dispneia, com cianose central. As saturações de oxigénio são inferiores a 92% no ar, com outras manifestações de hipoxia.
5. Crítica	Rápida progressão para síndrome de dificuldade respiratória aguda ou insuficiência respiratória, com ou sem choque, encefalopatia, lesão miocárdica ou insuficiência cardíaca, disfunção de coagulação e lesão renal aguda. As disfunções orgânicas podem ser fatais.

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ACE 2,8 may be lower in children than adults. Children are also more likely to have been recently exposed to other coronaviruses (four strains are identified: HCoV 229E, NL63, OC43 and HKU1) that are endemic worldwide and cause mild respiratory illnesses,⁹ which could provide some cross-protection against COVID-19. The immune response of children to SARS-CoV-2 is also likely to be different to adults. A less mature immune system does not explain the increased severity in infants compared with older children,⁶ but the smaller airways and immature respiratory tract could potentially contribute to more severe disease.

The role of children in the COVID-19 transmission chain remains unclear.¹⁰ So far, reports of asymptomatic children who are PCR positive for SARS-CoV-2 are mainly from contact tracing after a confirmed case, and they account for a small proportion of reported childhood cases. We urgently need population screening, seroincidence and seroprevalence studies to estimate age-specific asymptomatic infection rates in the community, which is critical for modelling and predicting disease transmission, as was done with influenza A (H1N1).¹¹ Such studies are currently underway (box 1), and their results will be important for informing policy decisions about school closures, lockdown and social distancing measures.

Whether pregnant women are at increased risk of COVID-19 - as with influenza A(H1N1) - is not clear. Neither is the risk of vertical transmission in utero nor during childbirth. There have been several reports of severe disease in pregnant women, including maternal deaths,¹² as well as intrauterine deaths, stillbirths and neonatal deaths.¹³ So far, there is no clear evidence of vertical transmission from infected mothers to the newborn,¹⁴ despite reports of SARS-CoV-2 positivity in neonates within 36 hours of birth.¹⁵

Larger, more detailed studies are needed, and these, too, are currently underway (box 1).

CHILDHOOD COVID-19 IN THE UK

On the frontline, paediatricians have been working hard to prepare for an influx of cases, developing and implementing new guidelines, agreeing treatment options, restructuring emergency departments, wards and isolation units—all this while supporting adults services that are already overwhelming hospitals nationally. In children, COVID-19 cases and hospitalisations increased rapidly since the second half of March although with smaller numbers than in adults. Currently, paediatricians are receiving multiple requests for providing data

Box 1 Ways in which Public Health England is working with national health service and academic partners to answer important questions about sars-CoV-2 transmission and COVID-19 disease in children

Clinical follow-up of laboratory-confirmed COVID-19 cases in children aged 29 days to <16 years (paed COVID)

Public Health England receives electronic notifications of all confirmed COVID-19 cases from National Health Service hospital laboratories through the Second Generation Surveillance System. Notified childhood cases in the surveillance age group are followed up with their general practitioners and hospital to determine whether they were hospitalised and, if so, the responsible paediatric consultant is then contacted to complete a short online clinical questionnaire for each case. Information collected includes clinical presentation, underlying comorbidities, investigations, intensive care requirements, treatment and outcome at hospital discharge.

In order to speed up data collection, paediatricians in England can directly report cases to PHE by emailing phe.paedcovid@nhs.net. If you would like more information about the surveillance, please contact Dr Shamez Ladhani at shamez.ladhani@phe.gov.uk.

Confirmed COVID-19 cases in children are also followed up using the same online clinical questionnaire in Wales (Jennifer.Evans7@wales.nhs.uk) and Northern Ireland (Sharon.Christie@belfasttrust.hscni.net).

Clinical follow-up of laboratory-confirmed cases in neonates up to 28 days of age

PHE is working with colleagues at the National Perinatal Epidemiology Unit and Imperial College London to conduct clinical surveillance of COVID-19 in neonates from birth up to 28 days of age through the British Paediatric Surveillance Unit (www.bpsu.org.uk).

Paediatricians across the UK and Ireland will receive weekly emails from the BPSU team to report whether they have managed a case of neonatal COVID-19 in the previous week.

Those confirming a case will be asked to complete a short clinical questionnaire. Further information about the BPSU surveillance is available online: <https://www.rcpch.ac.uk/bpsu-study-neonatal-complications-coronavirus-disease-covid-19#lead-investigators>. For more information about the BPSU surveillance, please contact: Dr Jenny Kurinczuk or Dr Chris Gale at bpsu-covid@ndph.ox.ac.uk. At the end of the surveillance, cases will be linked to a similar surveillance of COVID-19 in pregnant women and their babies, which is in progress through the UK Obstetric Surveillance System (UKOSS). Further information about the UKOSS surveillance is available online: <https://www.npeu.ox.ac.uk/ukoss/current-surveillance/covid-19-in-pregnancy>. For more information about the UKOSS surveillance, please contact Dr Marian Knight

Risk of vertical transmission during pregnancy (peri-COVID)

Public Health England is working with St. George's University of London to assess the risk of vertical transmission in pregnant women with confirmed COVID-19. This surveillance will aim to collect blood, throat swab, urine and stool samples from the pregnant women and, after childbirth, from the baby. Obstetricians and Neonatologists across England are asked to contact the peri-COVID team when they have a pregnant woman with COVID-19 who hasn't yet delivered. More information including the protocol, the Participant Information Leaflet and the Consent Form are available online: www.pericovid.com. The peri-COVID team can be contacted at: pericovid@sgul.ac.uk

Serosurveys in children

PHE is conducting several seroprevalence surveys that include children, using blood samples from a number of different sources. For more information, contact Dr Gayatri Amirthalingam at: gayatri.amirthalingam@phe.gov.uk

i. PHE Seroepidemiology Unit (SEU): the SEU archive is an opportunistic collection of residual sera samples from routine microbiological testing, submitted

Continued

Box 1 Continued

voluntarily each year from hospital laboratories throughout England; PHE has contacted all NHS trusts requesting their support by providing 10 serum samples per week to the PHE SEU.

ii. Royal College of General Practitioners Research and Surveillance Centre: residual sera are collected from children over 10 years of age and adults from approximately 100 GP practices across England participating in primary care research mainly for influenza surveillance.

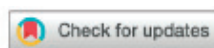
iii. What's The Story COVID-19: this serosurvey will build on an existing national research network and ethically approved NIHR-funded study to collect childhood and teenage serum samples for near real-time monitoring of increases in paediatric SARS-CoV-2 seropositivity rates across the UK in 2020. Paediatric hospitals can support the serosurvey by agreeing to provide residual serum samples from children having routine blood tests; this will ensure sufficient numbers of samples are collected across the childhood age groups.

on the same children with COVID-19. Some requests are important for managing healthcare resources and capacity, while others merely duplicate data that PHE is collecting as part of national surveillance. Given the relatively small number of childhood COVID-19 cases, the importance of centralised national reporting, data collection and dissemination is critical for establishing the true burden of disease in UK children and will allow more robust collaboration and comparisons with international cohorts in the future. PHE receives electronic notifications for all laboratory-confirmed COVID-19 cases in England and continues to contact paediatricians to request clinical information for hospitalised cases.

Paediatricians in the UK can facilitate the surveillance by proactively reporting cases to PHE by email (box 1). PHE is working to provide paediatricians with childhood COVID-19 data as quickly as possible.

In addition to providing surveillance data, paediatricians are encouraged to get involved with research and clinical

trials to better understand the immunopathophysiology and identify effective treatments for COVID-19 in children (<https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/>).



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Promoção e apoio à saúde e cuidados de saúde pediátricos durante a COVID-19 - Declaração da Posição da Associação Internacional de Pediatria

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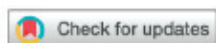
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The pandemic of COVID-19 disease caused by severe acute respiratory syndrome coronavirus and the risks it poses to families, communities and nations have led to massive social and economic consequences. While less likely to cause severe illness in healthy children or adolescents than adults, children can transmit the virus, and those under 1 year of age and with underlying comorbidities are at increased risk for more severe illness.¹

This paper provides recommendations from the International Pediatric Association for children's health and healthcare during COVID-19 (box 1). The IPA highlights the health needs of children and outlines priorities for preserving newborn, child and adolescent health during the COVID-19 crisis and beyond, where social distancing and lockdowns threaten access to routine care and preventive services. Our primary focus is on maintaining systems of primary care for children; however, much of this paper is also applicable to specialty and subspecialty care. We provide guidance for paediatricians and paediatric societies in managing children's general health needs, routine preventive care and well-being during the current school and daycare closures, social distancing and quarantines.

We recognise the need for specific strategies to reach those children and youth at greatest risk, including those in low-income and middle-income countries, as well as in fragile settings such as refugee camps. We address interim guidance on routine care and immunisation, preventing children from acquiring and transmitting infections, mitigating the consequences of social isolation and disruption of education, and ways paediatricians and children's services may organise remote delivery of care.

This paper does not attempt to provide definitive guidance for clinical management of children infected with or exposed to COVID-19, nor a comprehensive review of the evidence emerging about the virus and its effects. The science is evolving rapidly; current lay and technical guidance is available from the WHO (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>), the US Centres for Disease Control and Prevention (<https://www.cdc.gov/coronavirus/2019-nCoV/index.html>), the European Centre for Disease Prevention and Control (<https://www.ecdc.europa.eu/en/covid-19-pandemic>) and other competent bodies.

COVID-19

Severe acute respiratory syndrome-coronavirus-2 is a newly identified, highly contagious

pathogen that causes coronavirus 2019 disease (COVID-19).² It spreads quickly, primarily via droplets and fomites during close and unprotected contact. It can be spread by aerosol-generating procedures in healthcare settings and can persist on contaminated surfaces for several days.³ Common symptoms in adults include fever, tiredness and a dry cough.²

Children are less likely to present with these symptoms and may also have myalgias, nasal congestion, sore throat and diarrhoea.^{1,4} Symptoms are often mild, and more than 85% of infected adults recover without incident, but the remainder may become seriously ill and some die. More severe symptoms include difficulty in breathing, pneumonia, acute respiratory distress syndrome, and heart and kidney failure.² Older people, those with underlying medical problems, and smokers and e-cigarette users are more likely to develop severe disease.^{2,5}

Children are more likely to be asymptomatic shedders and are less likely to have severe disease than adults, although younger children and infants are more likely than older children to have severe disease.^{1,4} Limited evidence to date suggests that maternal to newborn vertical transmission, while rare, may occur.⁶ The WHO and other organisations note that there is no transmission of the virus through breast milk and advise preventing transmission by handwashing, cleaning the breast and using masks during breast feeding for COVID-19-infected mothers.⁷

PREVENTION OF COVID-19

Prevention of the spread of infection is of paramount importance to limit the burden of disease. Preventive measures to reduce transmission recommended by the WHO stress meticulous droplet and contact precautions, including enhanced hand hygiene, reduction of contacts among the general population (physical or social distancing) and isolation of patients with signs of the disease.⁸ Children and adults with asymptomatic or presymptomatic infection may transmit the infection to other individuals; thus, families in areas with active infections should be advised to avoid contact other than with immediate family members and to avoid social contacts and group gatherings. All family members, including children, should wash their hands frequently with soap and water for at least 20s, or use hand sanitiser. Family members with symptoms of fever or cough should stay home, with as much separation from other family members as possible.⁸

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Box 1 – Recomendações da Associação Internacional de Pediatria para a saúde e cuidados de saúde pediátricos durante a COVID-19

Prevenção e tratamento

- ▶ A maioria das crianças com a doença COVID-19 sem doença prévia, compromisso imunológico ou imunodeficiência, tem um curso de doença leve e pode ser isolada em casa. As crianças com doença mais grave devem ser tratadas em instalações capacitadas para prestar cuidados pediátricos. Devem ser tomadas precauções especiais para proteger as crianças com menos de 1 ano.
- ▶ Em ambientes de cuidados pediátricos, devem ser tomadas precauções para minimizar o risco de transmissão da síndrome respiratória aguda (SARS)-CoV-2. As recomendações da OMS para as precauções relativas às gotículas e ao contacto devem ser seguidas criteriosamente, incluindo o rastreio de risco antes e à entrada de unidades clínicas, a separação de crianças de baixo e alto risco, o uso de máscaras de proteção para o nariz e boca e vestuário de proteção por parte dos profissionais de saúde, lavagem minuciosa das mãos com sabão ou detergente e uso frequente de desinfetantes. Também devem ser seguidas as recomendações da OMS para uma amamentação segura em casos de mães infetadas com COVID-19, ou seja, lavagem das mãos, limpeza dos seios e uso de máscaras.
- ▶ Em áreas com elevada incidência de novas infeções por SARS-CoV-2, os pediatras devem incentivar as famílias com crianças a permanecerem em casa para reduzir ao máximo o contacto social para toda a família, a melhorarem a higiene pessoal através de uma lavagem regular e completa das mãos, a cobrir a tosse com o cotovelo em vez das mãos e a evitarem tocar no rosto.
- ▶ Com vista a minimizar a propagação da infeção, as sociedades pediátricas devem trabalhar em estreita colaboração com as autoridades de saúde pública de forma a disponibilizar informação e conselhos precisos aos médicos e ao público sobre estratégias de prevenção, testes e tratamento, sobre família, parentalidade e educação durante emergências de saúde pública e sobre sistemas de saúde e recomendações para as instalações. Este trabalho deve incluir estratégias para alcançar as populações especiais em situação de risco elevado, abordar as disparidades de acesso entre as populações nacionais e regionais e garantir a continuidade dos esforços para fornecer cuidados essenciais aos recém-nascidos e cuidados primários universais.
- As organizações pediátricas regionais e nacionais devem disponibilizar informação precisa e links para a OMS e outros recursos credíveis de forma a ajudar os profissionais de saúde e o público em geral a evitar terapias enganosas e relatórios falsos.
- Todos os interessados devem ser incentivados a usar o termo “distanciamento físico” em vez de “distanciamento social” para enfatizar a importância de se reduzir a propagação, reconhecendo simultaneamente o valor da proximidade social e do apoio psicológico.
- ▶ O desenvolvimento de vacinas e tratamentos para a COVID-19 deve incluir estudos sobre a eficácia do tratamento e da prevenção em crianças de todas as idades, para além dos adultos, e devem ser prontamente disponibilizados a crianças quando estiver preparadas a sua entrega em larga escala.

continua

Box 1 continua

Vacinas

- ▶ Todas as crianças devem continuar a ser vacinadas de acordo com a sua planificação habitual, com todos os anti-génios relevantes e sempre que possível.
- A decisão de manter ou suspender os serviços de imunização de rotina deve ter em consideração decretos locais de distanciamento físico e respostas dos sistemas de saúde, o estado atual e perspetivado de transmissão local de COVID-19 (por exemplo, sem casos e com transmissão esporádica, em grupo ou comunitária) e fatores que afetem as imunizações de rotina, incluindo a demografia populacional e os padrões migratórios.
- ▶ As sociedades pediátricas devem trabalhar com a OMS, a UNICEF, Grupos Técnicos e Consultivos de Programas Nacionais de Imunização e os governos na monitorização do atraso e interrupção dos planos de vacinação e sugerir planos para alcançar as metas, dependendo da sua situação a nível local e nacional.
- A vigilância de doenças preveníveis por vacinação deve ser mantida e reforçada para permitir a deteção e gestão precoce dos casos e, sempre que possível, contribuir para a vigilância da COVID-19.
- Devem ser planeadas campanhas de sensibilização com especial atenção às populações que necessitam de vacinação de rotina contra doenças como o sarampo, a febre amarela e a difteria.
- ▶ O planeamento da imunização deve incluir estratégias de comunicação eficazes e o envolvimento com as partes interessadas e comunidades para dissipar as preocupações e melhorar, manter ou restabelecer a procura de vacinação por parte da comunidade

Telemedicina

- ▶ As sociedades pediátricas devem defender políticas que incentivem e facilitem a prestação de serviços de telemedicina ou de teleconsultas para satisfazer as necessidades das famílias durante a pandemia, com estratégias para abordar as disparidades no acesso à telemedicina e para equilibrar o aumento do acesso, evitando danos decorrentes de diagnósticos errados ou de limitações no conforto do doente e do clínico ou da tecnologia disponível.

The most vulnerable groups of the population are advised to stay at home for as long as there is a high risk of infection. These include transplant recipients and people with leukaemia or lymphoma, on immunosuppression therapy, with severe respiratory conditions including cystic fibrosis or asthma, or with diseases or inborn errors of metabolism.⁸ Children and adults are also at increased risk of infections in densely crowded conditions such as in refugee camps and jails or detention centres; in families living in extreme poverty, without basic water, sanitation and hygiene resources; and in countries with limited access to health services. Support from donor governments and others will be needed to strengthen health systems and to implement strategies to prevent transmission in low-income and middle-income countries, as well as in fragile settings.⁹

The WHO and government health agencies have published guidelines to help prevent transmission to health workers and patients in healthcare settings.^{8 10 11} Healthcare settings should adhere strictly to hygiene and precautionary measures to avoid close contact between patients and should avoid droplet exposure through use of personal protective equipment (PPE). Patients with symptoms of respiratory infection or known COVID-19 contacts should be isolated and separated from children without symptoms. Limitations on visitors and accom-

panying persons and physical distancing between patients are also recommended. Healthcare professionals with symptoms should stay home and seek diagnostic testing if available because COVID-19 among staff members can contribute to rapid spreading of virus. Healthcare professionals are at increased risk of becoming infected; thus, strategies to ensure availability, safe procedures and proper use of PPE are essential. The epidemic has overwhelmed the capacity of many healthcare systems and has led to shifting of resources from children to adult services and to delaying or cancelling elective procedures for all ages.

THERAPEUTIC AND PREVENTIVE AGENTS

Current treatment for COVID-19 is supportive care. While home-based care is preferable for children with mild–moderate signs, more severely ill children should be hospitalised and monitored and assessed for other sources of infection, even if they are suspected or confirmed to have COVID-19 infection. Additional guidance for management of severe acute respiratory disease is available from the WHO.¹¹

Numerous trials for treatment and prevention or postexposure prophylaxis are under way, but evidence on effective treatments is not yet available; thus, use of specific drugs should be under medical and regulatory supervision to establish safety and efficacy. Paediatric organisations should advocate for rapid inclusion of children in clinical trials once promising initial individual therapies are in efficacy trials. Similarly, there are clinical trials under way to develop covid-19 vaccines. Paediatric organisations should support GAVI: the Vaccine Alliance, the WHO, the UNICEF and others working to plan adequate scale-up of production and delivery. Advocacy is needed to encourage vaccine efficacy trials to include people of all ages, children with special needs and others who are especially at risk.

Avoiding rumors and sham treatment

In times of crisis, rumours and false stories shared via social media can go viral and create disinformation.¹² Paediatricians and other clinicians should be cautious about starting therapies based on news or social media reports, and should rely on trusted sources of evidence-based information and share those with the families in their care. Major medical journals have accelerated rapid reviews and publication schedules, relaxing embargo policies and making all COVID-19-related content available freely online without paywall or subscription barriers.¹³

It is equally important that families be aware that many sham remedies have been promoted to the public. Many sham treatments have been widely disseminated on social media. Some have been shown to be harmful; none have been proven effective at prevention or treatment and thus should not be recommended.¹⁴ These include, for example, drinking warm water, saline or garlic gargles, drinking lemon juice with honey or black seeds, use of specific homeopathic or alternative medicines, and drinking specific alcoholic drinks.¹⁴

Vaccines and other essential services during COVID-19

The WHO has issued guidance for immunisation activities and for maintaining essential health services during an outbreak, identifying immunisation as a core health service that should be prioritised and safeguarded during the epidemic.⁸

As detailed by WHO's Strategic Advisory Group of Experts on Immunisation, mass vaccination campaigns should be temporarily postponed to follow recommendations on physical distancing and ensure delivery of immunisations does not contribute to COVID-19 spread.¹⁵ However, planning and catch-up efforts should be addressed rapidly, with attention to preventive strategies for vulnerable populations at increased risk of morbidity and mortality from outbreak-prone diseases.¹⁵

Similarly, essential nutritional interventions, access to healthy foods and other strategies to prevent maternal, newborn

and child mortality and to maintain care systems should be maintained as much as possible during the emergency response, and modifications and delays should be explicitly planned and managed to safely maintain essential service and healthcare delivery. Immunisation and other delivery strategies in clinical settings should be adapted and conducted under safe conditions, without undue risk to health workers, caregivers or the community.⁸

CARE DELIVERY AND TELEMEDICINE

The WHO and others have also issued recommendations on maintaining children's well-child visits during the pandemic.⁸ Physical distancing requirements may disrupt routine care, and many parents are afraid to leave their homes or do not want to take their child to a clinic where sick children might be present. Families commonly pass information to their paediatrician over the phone, by email or by social media applications. Expansion of more formal telemedicine protocols can help address continuity of care during COVID-19, although with some limitations due to disparities in internet access and language or cultural barriers to alternate care modalities.

Telemedicine facilitates use of alternatives to face-to-face encounters and may include online visits, live video conversations, store and forward technology, mobile health applications and messaging through text or email.^{16,17} Telemedicine is a useful tool for long-distance clinical care and can be used for education, counselling parents and health management.¹⁶

With appropriate attention and caution for issues of patient safety, confidentiality and accountability for missed diagnoses, telemedicine can be an effective way to help patients during the COVID-19 pandemic.^{17,18} The British Medical Journal and the American Academy of Paediatrics (AAP) have offered guidance on structuring practice for teleconsulting¹⁹ and telemedicine²⁰ during the pandemic. Paediatric societies should advocate for immediate legal, regulatory and reimbursement system actions to facilitate integrating telemedicine for routine well, acute and chronic paediatric care while supporting social distancing and other changes designed to prevent the spread of COVID-19.¹⁸

Caring for children and families and clinicians

Many families are struggling with children being out of school or parents being out of work during the pandemic. Children and adolescents may be stressed, and may not have the emotional or psychological resources to cope with the many changes occurring.²¹ Fear of exposure and self-quarantine or social distancing strategies create anxiety and uncertainty, at the same time impacting social support systems. Changes in family work and income may lead to food and housing instability, interpersonal violence, unintentional injury, child abuse or other adverse childhood events, especially for those who are most vulnerable.²¹ The WHO, UNICEF and others have developed guidance for families, and paediatricians can help support families who are stressed to help them address changing parenting needs and ways to explain the pandemic to their children.^{21–23} Other resources include AAP's positive parenting²⁴ and the Inter-agency Network for Education in Emergencies COVID-19 site.²⁵ Healthcare workers face additional stressors because of the danger of infection, shortages of PPE, fear of bringing infection home, witnessing coworkers becoming ill and having to make decisions about scarce resources. Professional societies should identify and disseminate recommendations to help manage these stressors through attention to self-care, use of cognitive coping strategies, and encouraging efforts to maintain social networks and support. Numerous regional and national paediatric societies have issued recommendations (selected links are included in box 2); all national paediatric societies should provide or link to resources to help their members and families identify reliable information sources during the epidemic.

Box 2 Resource links on COVID-19 and child health

- ▶ COVID-19 page on the International Pediatric Association website: <https://ipa-world.org/covid-19-news-and-updates.php>
- ▶ WHO covid resource pages: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
- ▶ UNESCO: <https://en.unesco.org/themes/education-emergencies/coronavirus-school-closures>
- ▶ European Centres for Disease Control: <https://www.ecdc.europa.eu/en/coronavirus>
- ▶ US Centers for Disease Control and Prevention: <https://www.cdc.gov/coronavirus/2019-nCoV/index.html>
- ▶ Société Française de Pédiatrie: <https://www.sfpediatric.com>
- ▶ Asociación Latinoamericana de Pediatría: <https://alape.org>
- ▶ Canadian Paediatric Society: <https://www.cps.ca/en/tools-outils/covid-19-information-and-resources-for-paediatricians>
- ▶ American Academy of Paediatrics: <https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections>
- ▶ Indian Academy of Paediatrics: www.iapindia.org
- ▶ European Society for Paediatric Research: <https://www.espr.eu/news/news-detail/COVID-19-Resources-from-Pediatric-Research/177>
- ▶ REACTing Research and Action: <https://reacting.inserm.fr/literature-review/>
- ▶ UK Royal College of Paediatrics and Child Health guidance for paediatric services: <https://www.rcpch.ac.uk/resources/covid-19-guidance-paediatric-services>
- ▶ Resource materials from the Coalition of Centres in Global Child Health: <https://www.gchcoalition.com/covid-19.html>
- ▶ Covid-19 information for paediatric surgeons: <https://www.baps.org.uk/professionals/covid-19-information-for-paediatric-surgeons/>
- ▶ German Society for Paediatrics Coronavirus Information: <https://www.dgkj.de/fachinformationen-corona-virus>
- ▶ International Society for Paediatric and Adolescent Diabetes: <https://www.ispad.org/news/494473/COVID-19-and-Childrenwith-Diabetes.htm>

INTERNATIONAL PEDIATRIC ASSOCIATION (IPA) RECOMMENDATIONS

The IPA is a membership organisation of 169 paediatric societies, which includes 144 national paediatric societies, 10 regional paediatric societies and 13 international paediatric specialty societies. The IPA believes that every child should be accorded the right to the highest attainable standard of health and the opportunity to grow, develop and fulfil their potential. IPA is a collaborating organisation of the WHO and advocates for child health as the voice of paediatric professional organisations at WHO's Partnership for Maternal and Child Health and the UNICEF.

IPA calls on our member paediatric societies to address children's health and healthcare during the COVID-19 pandemic. Primary care and hospital resources for children and youth must be maintained during the epidemic, both to ensure ongoing child and adolescent health priorities are addressed and to provide services for children with more severe COVID-19 disease. National paediatric societies should provide appropriate evidence-based resources to help their members and families navigate reliable information during the epidemic; these should be updated as emerging evidence is incorporated into the WHO's guidance. IPA strongly encourages communication and exchange of technical guidance among regional and

national paediatric societies, as well as close collaboration in research and in exchange of experiences. Regional and national paediatric societies are also urged to make COVID-19-related materials available freely on their websites. To facilitate this, we have established a COVID-19 page on the IPA Website²⁶ (<https://ipa-world.org/covid-19-news-and-updates.php>) and will periodically update links to resource materials and recommendations on that site. IPA encourages all paediatric societies to identify and disseminate recommendations and provide or link to resources to help our societies and their members identify and use reliable information, and to help the families of the children we care for get the care they need.

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A exposição precoce ao fumo de incêndio de minas de carvão e ao fumo de tabaco afeta a função vascular subclínica

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RESUMO

Objetivo Avaliar se a saúde vascular em crianças estava associada à exposição a um episódio de 6 semanas de fumo de incêndio de minas de carvão ou fumo de tabaco ambiental (FTA) num estudo de coorte retrospectivo.

Métodos Três anos após um incêndio de uma mina de carvão em Victoria, Austrália, investigamos a saúde vascular de crianças tanto *in utero* (n=75) ou com <2 anos de idade (exposição pós-natal, n=96) no período do incêndio. Os resultados foram a espessura da carótida íntima-média (IMT) e a velocidade de onda de pulso (VOP). A média e o pico diário de partículas em suspensão <2,5 µm de diâmetro (PM_{2.5}) foram estimados com base na sua localização diária durante o período de incêndio. Foram utilizados modelos de regressão linear multivariada para testar as associações entre as PM_{2.5} relacionadas com o incêndio e os resultados ajustados para as covariáveis relevantes, incluindo FTA.

Resultados No grupo de exposição pós-natal, cada aumento de 10 µg/m³ no nível médio de PM_{2.5} esteve positivamente associado de forma independente à VOP (β=0,116, p=0,028). Quando estes dois grupos foram combinados, observou-se uma associação entre a média de PM_{2.5} e o aumento da VOP em crianças com exposição a FTA (β=0,148, p=0,033) ou com mães fumadoras (β=0,151, p=0,011), mas não nas crianças não expostas a FTA ou ao tabagismo materno.

Conclusões Três anos após um incêndio numa mina de carvão, as crianças até 2 anos no momento da exposição apresentam um aumento da rigidez vascular. Embora não tenham sido observados efeitos adversos no grupo de exposição *in utero*, é necessário um estudo de seguimento adicional para esclarecer os efeitos a longo prazo da exposição ao fumo de incêndio de uma mina de carvão.

INTRODUCTION

Air pollution, including the airborne particulate matter <2.5 µm in diameter (PM_{2.5}), is associated with impaired vascular function, especially for individuals at higher risk, such as diabetes, or age, either older or younger.¹⁻³ In children, parental smoking^{4,5} and exposure to traffic emissions³ have been associated with reduced vascular function, and in utero exposure to air pollution has been linked with increased carotid artery stiffness in young adults.⁶ However, evidence of cardiovascular outcomes in children exposed to an intense but time limited episode of poor air quality like coal mine fire smoke in early life is sparse. Any interplay with maternal cigarette smoking during pregnancy or environmental tobacco smoke (ETS, ie, a family member smokes at home) is also unknown.

Cardiovascular disease is rarely manifest in childhood, yet the origins can root during the early stages of life.⁷ Many risk factors can accelerate the development of cardiovascular disease in children, including genetic predis-

What is already known?

- Exposure to outdoor air pollution like airborne particulate matter <2.5 µm in diameter (PM_{2.5})
- Environmental tobacco smoke (ETS) in early life is linked to poorer vascular health in children.

What is already known?

- In infants aged up to 2 years at the coal mine fire period, PM_{2.5} exposure during the fire was associated with increases in vascular stiffness
- Early life PM_{2.5} exposure during the fire was associated with higher vascular stiffness in children whose mothers smoked during pregnancy or were exposed to ETS.

position, exposure to tobacco smoke, obesity and increased sedentary activities.⁸ The structural change of vascular is an early indicator of the development of cardiovascular disease. Lipid deposition along the intima can be seen in nearly all children by 3 years of age.⁹ Arterial stiffness gradually increases with age, and plays an important role in the pathogenesis of cardiovascular outcomes.¹⁰

Given the limited available evidence regarding children's exposure to air pollution episodes, the Latrobe early life follow-up (ELF) study¹¹ was established to follow the health and development of children following a coal mine fire. Here, we examine possible associations between exposure to coal mine fire emissions and vascular health 3 years after the fire.

METHODS

Study design

The Latrobe ELF cohort study forms one stream of the Hazelwood Health Study (HHS).¹¹ The HHS was established to investigate possible health effects of air pollution from a fire in the Hazelwood open cut coal mine in 2014 in the Latrobe Valley of Victoria, Australia. The fire caused elevated concentrations of PM_{2.5} and other air pollutants for nearly 6 weeks, affecting many nearby communities. The ELF study aims to understand possible associations between exposure to the mine fire smoke and the health and development of children who were aged less than <2 years, or whose mothers were pregnant at the time of the fire.

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Participant recruitment

All children whose parents completed the ELF baseline survey¹¹ and consented to clinical testing were invited to participate in testing of vascular structure and function 3 years after the fire. The details of participant recruitment are outlined in online supplementary data S1.

Data collection

Demographic characteristics and health-related risk factors

The collection of demographic characteristics and health-related risk factors are outlined in online supplementary data S2.

Exposure allocation

The Hazelwood mine fire smoke exposure period was from 9 February to 31 March 2014. Participants were classified into two groups based on their mother's estimated date of conception and the fire period:

1. The postnatal exposure group included children born between 1 March 2012 and 9 February 2014 and aged <2 years at the time of the fire.
2. The in utero exposure group comprised children who were in utero or born during the fire period, which was determined by the date of conception or birth. Their mothers had been pregnant and resident in the Latrobe Valley at the time of the fire.

Our collaborators at the Commonwealth Scientific and Industrial Research Organisation implemented meteorological and chemical transport modelling to estimate hourly PM_{2.5} concentrations at a spatial resolution of 1×1 km. Further details about the exposure modelling can be found on the HHS website.¹² The mean and peak 24 hours PM_{2.5} exposure during the fire period for each participant were calculated based on their reported night and day locations during the fire period. Information about their daily time activity patterns during the fire period was collected in the baseline questionnaire.¹¹

Outcome measures

The outcomes were two non-invasive tests for early markers of atherosclerosis: (1) carotid intima-media thickness (IMT) and (2) pulse wave velocity (PWV). Increases in either of these measurements are associated with the subsequent cardiovascular risk.^{13 14} The detailed methods of outcome assessment are outlined in online supplementary data S3.

Statistical analysis

Sociodemographic and vascular characteristics of the study participants and their parents were expressed as mean±SD or percentage. The associations between exposure to the mine fire emissions and vascular health were examined in the study participants, with separate analyses of the postnatal and in utero exposure groups. Multivariable linear regression models were used for independent associations between the vascular outcomes, and daily mean and peak PM_{2.5} exposures during the fire period.

We report results per 10-unit increase in mean PM_{2.5} (µg/m³), and per 100-unit increase in peak PM_{2.5}, which were close to the IQRs of each exposure metric. A group of covariates extracted from the baseline survey data known to be determinants of, or potentially related to, vascular outcomes were selected as a priori in our initial models. We retained all variables that influenced the outcome by 10% or more. These were children's age, birth weight, maternal education attainment, maternal smoking status in pregnancy, ETS and parental diabetes. Retention of the other covariates did not meaningfully influence the results. Accordingly, a multivariable model was adjusted for children's age, birth weight, maternal educational

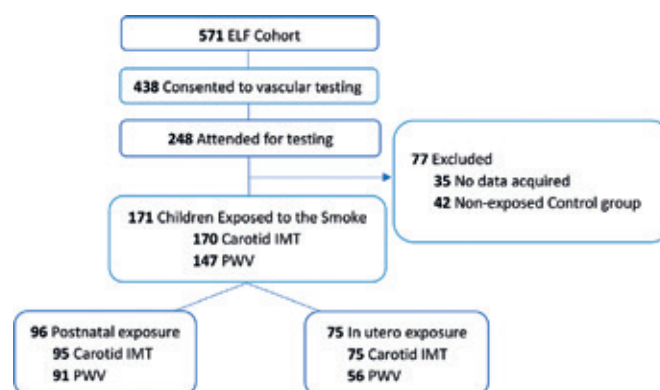


Figure 1 Flow diagram of participants in vascular assessment. IMT, intima-media thickness; PWV, pulse wave velocity.

attainment, maternal smoking status in pregnancy, ETS and parental diabetes.

ETS was defined as the presence of a current smoker, including the mother, in the child's household. In addition, subgroup analyses were conducted separately for the children with exposure to ETS and whose mothers smoked tobacco during pregnancy adjusted for children's age, birth weight, maternal educational attainment and parental diabetes. Diagnostic checks on the residuals were performed to assess model assumptions (online supplementary figure S1); 3.5% of the participants had missing data across any of the covariates (n=6), who were excluded from the multivariable regression. All data analyses were conducted using SPSS Statistics V.23 (IBM, Armonk, New York, USA).

RESULTS

Description of participants and vascular assessment

There were a total of 248 children who participated in this round of vascular testing, of whom 213 (86%) were able to complete at least one of the assessments. A total of 171 children exposed to coal mine fire smoke either in utero (n=75), or in their first 2 years of life (n=96) were studied (figure 1). The sociodemographic and vascular characteristics of the children are summarised in table 1.

Nearly 99% of the children were born in Australia. The sex distributions were similar in the postnatal and in utero groups. The age differences between groups were due to the classification of their exposure by age. The proportions of children with maternal tobacco smoking during pregnancy and ETS were slightly higher in the postnatal than the in utero exposure group. The distributions of the mean and peak 24 hours PM_{2.5} exposure during the mine fire period by the exposure groups are illustrated in figure 2.

Associations between fire smoke emissions and vascular outcomes

The results of univariable and multivariable linear regression models to examine the association between daily mean PM_{2.5} exposures during the fire period and vascular outcomes for different exposure groups are presented in table 2. The results for peak PM_{2.5} are outlined in online supplementary table S1. There was no association between either the mean or the peak PM_{2.5} exposures and vascular measurements in all children exposed either in utero or during their infancy. No significant associations between PM_{2.5} exposure and carotid IMT were observed in any of the models and subgroup models. However, when the in utero and postnatal exposure groups were evaluated separately, a slightly different picture emerged for each group as follows:

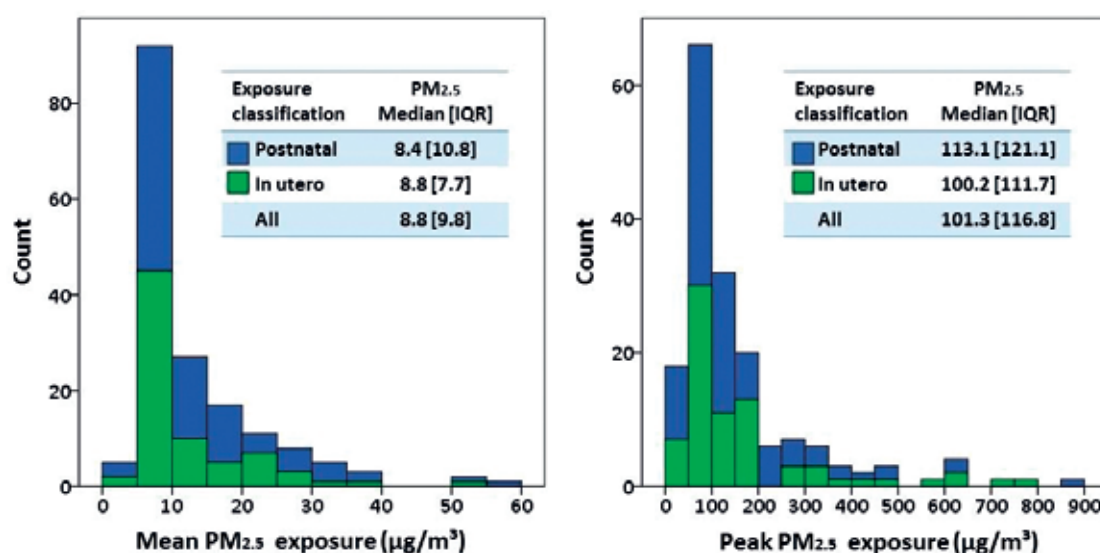


Figure 2 Distribution of estimated mean (left) and peak (right) 24 hours PM_{2.5} exposure during the mine fire period by exposure group. PM_{2.5}, particulate matter <2.5 µm in diameter. a The analyses did not include control group. Children who were not exposed to the fire smoke have age differences from the older children in the exposure group.

Factors associated with vascular outcomes in the postnatal exposure group

In the postnatal exposure group (n=96), each 10 µg/m³ increase in mean PM_{2.5} exposure was independently associated with an increase in PWV of 0.116 m/s (95% CI 0.013 to 0.218; p=0.028) (table 2). The result for the association between each 100 µg/m³ increases in peak PM_{2.5} exposure and PWV was in the same direction but not statistically significant (0.067, 95% CI -0.008 to 0.143, p=0.08) (online supplementary table S1). There was no collinearity in these models (variation inflation factor <2).

Demographic characteristics and health-related risk factors

We did not find any associations between exposure to fire smoke and any markers of vascular health in the in utero exposure group (n=75). In this group, however, maternal tobacco smoking during pregnancy was associated with thicker carotid IMT (0.52±0.03 vs 0.49±0.03 mm, p=0.012) (online supplementary figure S2). The association was independent of PM_{2.5} exposure (either mean or peak), parental diabetes, children's age, birth weight and maternal education level (mean PM_{2.5} p=0.032; peak PM_{2.5} p=0.029).

Demographic characteristics and health-related risk factors

There were no associations between mean or peak PM_{2.5} exposures and PWV or IMT in children without exposure to ETS or whose mothers did not smoke during pregnancy. However, we observed statistically significant associations between coal mine fire smoke exposure level and higher PWV in the subgroup of children with exposure to ETS or whose mothers smoked during pregnancy. The details are outlined in online supplementary data S4.

DISCUSSION

In this cohort study, higher mean PM_{2.5} exposure during the mine fire period was associated with increased PWV in the postnatal exposure group who were aged up to 2 years at the time of the fire, but not with any measures of arterial thickness. No associations between PM_{2.5} exposure and any vascular outcome were observed in the in utero exposure group. Early life exposure to PM_{2.5} during mine fire period was also associated with higher PWV in the 14.6% of children with a history of maternal tobacco smoking in pregnancy and the 21.1% of children with exposure to ETS. These findings were in a relatively small subgroup of children. However, smoking during pregnancy and childhood exposure to ETS are well-established risk factors for the reduced vascular health of chil-

dren and it is plausible that it could increase the sensitivity to adverse impacts of other sources of air pollution.^{15 16} We also observed that maternal tobacco smoking during pregnancy was independently associated with higher carotid IMT in the in utero exposure group in this study.

We are not aware of other studies that have investigated for possible influences of early life exposure to smoke from landscape fires on vascular stiffness in young children. In previous studies of adults, there is wide variation in the types of air pollution studied, sample sizes, study designs and study populations.

For example, one double-blind randomised study involving 12 healthy men found that acute exposure to diesel exhaust was associated with increasing arterial stiffness.¹⁷ Another randomised, crossover study with older adults demonstrated that PWV was decreased after walking in less polluted areas, but the benefit was reduced when walking on streets with high traffic-related air pollution.¹⁸

Tobacco smoking during pregnancy has been associated with long-term impairment of children's cardiovascular health,¹⁹ higher carotid artery IMT¹⁶ and higher blood pressure and reduced cardiac function in children aged 6 years.²⁰ Other cardiovascular effects documented to date have included a greater risk of atherosclerotic lesions, higher cholesterol levels and higher systolic blood pressure in childhood.^{21 22} Similarly, studies have shown that exposure to ETS in early life increases the risk of adverse vascular health outcomes including greater carotid IMT and atherosclerotic plaque formation in adulthood.^{4 5} These results are consistent with our findings about the associations between maternal tobacco smoking during pregnancy and higher IMT in children.

The development of cardiovascular disease in children exposed to tobacco smoke in early life may follow a different physiological trajectory. The adverse fetal environment with maternal smoking has been associated with fetal blood flow adaptations,²³ increased arterial stiffness²⁰ and enduring changes to blood pressure regulation.¹⁹ Both epidemiological and experimental studies have shown the adverse effects of prenatal and postnatal exposure to tobacco smoke on cardiovascular systems.²⁴ It is possible that such changes could lead to different reactions and a decreased ability to adapt to later environmental insults such as that produced by the coal mine fire smoke.

The strengths of our study include the detailed and personalised individual PM_{2.5} exposure estimates. Furthermore, a wide range of potential risk factors, confounders and effect modifiers for vascular outcomes via comprehensive information were collected in the baseline survey. We used state-of-the-art vascular

Table 1 Sociodemographic and vascular characteristics of participants categorised by exposure group

	Exposure classification		
	Postnatal n=96	In utero n=75	All n=171
Child's age (months)	50.9±6.5	34.5±3.0	43.7±9.7
Height (cm)	106.3±6.4	94.1±4.1	101.0±8.2
Weight (kg)	19.4±4.7	14.9±1.5	17.4±4.3
BMI (kg/m ²)	17.0±2.5	16.8±1.1	16.9±2.0
Birth weight (g)	3435±597	3491±478	3460±547
Gestational age (week)	39.6±1.8	39.3±1.7	39.5±1.8
Maternal age (years)	28.7±5.8	30.7±4.4	29.6±5.3
Carotid IMT (mm)	0.499±0.03	0.493±0.034	0.497±0.034
PWV (m/s)	4.12±0.45	4.20±0.48	4.15±0.46
Male	49 (51.0)	37 (49.3)	86 (50.3)
Child's country of birth			
Australia	95 (99.0)	74 (98.7)	169 (98.8)
Other	1 (1.0)	1 (1.3)	2 (1.2)
Breastfeeding status			
Breast fed until 3 months of age or less	31 (32.3)	23 (30.7)	54 (31.6)
Breast fed longer than 3 months of age	63 (65.6)	51 (68.0)	114 (66.7)
Not stated	2 (2.1)	1 (1.3)	3 (1.8)
Maternal cigarettes smoking status in pregnancy	17 (17.7)	8 (10.7)	25 (14.6)
Exposure to environmental tobacco smoke	23 (24.0)	13 (17.3)	36 (21.1)
Maternal alcohol consumption in pregnancy	9 (9.4)	7 (9.3)	16 (9.4)
Maternal highest level of education			
Year 12 or below	38 (39.6)	17 (22.7)	55 (32.2)
Postsecondary	58 (60.4)	57 (76.0)	115 (67.3)
Not stated	0 (0)	1 (1.3)	1 (0.6)
Maternal stress in pregnancy			
Hardly ever/sometimes stressed	84 (87.5)	63 (84.0)	147 (86.0)
Stressed often/nearly all of the time	12 (12.5)	10 (13.3)	22 (12.9)
Not stated	0 (0)	2 (2.7)	2 (1.2)
Mine fire on maternal stress			
Stress not affected/increased a little	59 (61.5)	47 (62.7)	106 (62.0)
Stress increased a lot	36 (37.5)	25 (33.3)	61 (35.7)
Not stated	1 (1.0)	3 (4.0)	4 (2.3)
Parental major adverse cardiovascular events	2 (2.1)	1 (1.3)	3 (1.8)
Parental hypertension	19 (19.8)	9 (12.0)	28 (16.4)
Parental diabetes mellitus	6 (6.3)	7 (9.3)	13 (7.6)
Parental high cholesterol	13 (13.5)	7 (9.3)	20 (11.7)

*Data are mean±SD or n (%).

IMT, intima-media thickness; PWV, pulse wave velocity.

measurements. This included automatic contour detection of IMT, which provides a more accurate and objective result than manual measurements.²⁵ The applanation tonometry in our PWV measurements is the gold standard for assessing arterial stiffness.²⁶

However, our study has several limitations. The information from the baseline survey relied on parents' or carers' self-report of medical conditions and lifestyle factors rather than medically verified diagnoses. Furthermore, data for children who were not exposed to the fire smoke episode at any stage could not be compared directly with the results from the older children in the exposure group because of age differences. The control group will become old enough to be an appropriate age-matched comparison group in the second round of clinical testing, which is currently planned for 2020. Reanalysis at that time will be important to confirm these initial findings. In addition, the results from the subgroup analyses of those with maternal tobacco smoking or ETS should be interpreted carefully as the sample size was small and thus hypothesis generating. However, these findings are consistent with previous literature of harmful effects of ETS.^{4 5 15}

There is normal variation in vascular measures in children, so these results do not mean that children with higher vascular stiffness or thickness will necessarily develop cardiovascular problems. Vascular health in childhood is one of many risk factors, such as genetic make-up, smoking tobacco, stress, diet

Table 2 Univariable and multivariable association between mean PM_{2.5} exposure during the fire period and vascular outcomes by exposure group

	Postnatal		In utero	
	Univariable	Multivariable*	Univariable	Multivariable*
Carotid IMT (β† (95% CI))	−0.001 (−0.006 to 0.005)	−0.001 (−0.007 to 0.005)	0.002 (−0.007 to 0.011)	0.001 (−0.009 to 0.011)
PWV (β† (95% CI))	0.044 (−0.036 to 0.124)	0.071† (−0.015 to 0.156)	−0.044 (−0.189 to 0.101)	−0.057 (−0.218 to 0.105)

*Models were adjusted for maternal smoking status during pregnancy, ETS, parental diabetes, children's age, birth weight and maternal education level.

†The β value for each variable represents the change per 10 µg/m³ increase in mean PM_{2.5}. Bold p<0.05.

#Model was adjusted for maternal smoking status during pregnancy, ETS, parental diabetes, children's age, birth weight, maternal education level and whether the participants were in the postnatal and in utero group.

ETS, environmental tobacco smoke; IMT, intima-media thickness; PM_{2.5}, particulate matter <2.5 µm in diameter; PWV, pulse wave velocity.

and physical activity, which can influence the risk of cardiovascular disease in later life.⁸ Furthermore, many factors including socioeconomic disadvantage and lower health literacy are associated with smoking and other environmental and lifestyle risk factors which could impact on cardiovascular risk in children.^{27 28} However, the existing literature and the results from the ELF study demonstrate the importance of reducing exposure to tobacco smoke in unborn babies and children because of the large influence this has on shaping children's health.

CONCLUSIONS

In summary, we found no associations between mine fire exposure and vascular health in the two groups combined nor the in utero exposure group. Although no adverse effects were observed in the in utero exposure group, further follow-up study is needed to elucidate the long-term effects of coal mine fire smoke exposure.

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Contributors All authors involved in the design and planning of the study. Participant recruitment was conducted by FHJ and MD. BZ, TO'S, GJW, SM and KN involved in data collecting, processing and reporting. BZ drafted the first manuscript. FHJ, SM, MD, AV and KN revised the entire manuscript critically. All authors approved the final version for publication. KN is guarantor for the study.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data sets used for the current study are securely held by Latrobe ELF study and cannot be shared by the authors. Relevant and only anonymised data can be available from project manager on reasonable request.

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Telerreabilitação pulmonar supervisionada versus reabilitação pulmonar em DPOC grave: um ensaio multicêntrico aleatorizado

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RESUMO

Fundamentação A reabilitação pulmonar (RP) é um tratamento padrão essencial e eficaz em pessoas com DPOC. No entanto, reportam-se uma fraca adesão de participantes, uma comparência insuficiente e elevadas taxas de abandono. Justifica-se uma investigação dos benefícios alcançados através de abordagens alternativas, tal como a telerreabilitação pulmonar (TRP).

Objetivo De modo a investigar se a TRP é superior à RP convencional relativamente ao exame de distância de caminhada durante 6 minutos (6MWD, do inglês *6-minute walk distance*) e, em termos secundários, aos sintomas respiratórios, à qualidade de vida, à atividade física e à função muscular dos membros inferiores em doentes com DPOC e FEV₁ <50% elegíveis para RP de rotina em ambulatório de base hospitalar.

Métodos Neste ensaio de ocultação simples, multicêntrico, com superioridade, aleatorizado e controlado, os doentes foram distribuídos num rácio de 1:1 para 10 semanas de TRP por grupos (60 min, três vezes por semana) ou RP convencional (90 min, duas vezes por semana). As avaliações foram realizadas por avaliadores ocultados no início do estudo, no final da intervenção e às 22 semanas de seguimento desde o início do estudo. A análise primária foi baseada no princípio de intenção de tratar.

Medições e principais resultados O resultado primário foi a alteração da 6MWD desde o início do estudo até às 10 semanas. Foram incluídos e aleatorizados 134 participantes (74 mulheres, idade média ± DP de 68 ± 9 anos, FEV₁ estimado de 33% ± 9%, 6MWD de 327 ± 103 metros). A análise não apresentou quaisquer diferenças entre grupos em termos de alterações da 6MWD após intervenção (9,2 metros [95% IC: -6,6 a 24,9]) ou às 22 semanas de seguimento (-5,3 metros [95% IC: -28,9 a 18,3]). Mais participantes completaram a intervenção de TRP (n=57) do que de RP convencional (n=43) (teste χ^2 p<0,01).

Conclusão A TRP não foi superior à RP convencional em termos da 6MWD e não foram descobertas diferenças entre os grupos. À medida que mais participantes completarem a TRP, será relevante comparar a TRP supervisionada com a RP convencional num desenho de estudo de não inferioridade.

Número de registo do ensaio ClinicalTrials.gov(NCT02667171), 28 de janeiro de 2016.

INTRODUCTION

Pulmonary rehabilitation (PR) is recognised as an important, standard treatment for people with chronic obstructive pulmonary disease (COPD). PR is well documented to reduce symptoms and increase walking capacity and quality of life (QoL), but its effect on physical activity level (PAL) is limited.^{1–5} Despite the

Mensagens-chave

What is the key question?

► Can a supervised pulmonary tele-rehabilitation programme, including structured exercise and education, deliver higher programme adherence and thereby superior benefits to a conventional hospital-based pulmonary rehabilitation (PR) programme for patients with severe COPD?

What is the bottom line?

► This pulmonary tele-rehabilitation model demonstrated short-term and medium-term improvements in functional capacity and disease-related symptoms that were not superior to conventional hospital-based PR for patients with severely progressed COPD.

Why read on?

► Despite the benefits, PR programmes are challenged by low participant uptake, insufficient attendance and high drop-out rates; supervised pulmonary tele-rehabilitation may be a useful second-line option to improve access for patients with severe COPD who cannot participate in or comply with a conventional hospital-based PR programme.

benefits, PR programmes are challenged by low participant uptake, insufficient attendance and high drop-out rates.^{6–9}

Barriers have previously been reported, including transportation issues, symptom severity, acute exacerbations, lack of energy and disruption of daily routines.^{6–8,10,11} Recently, the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommended investigating alternative approaches to PR, such as tele-rehabilitation, in an attempt to increase uptake and make PR available to more patients.¹² To date, two randomised controlled trials (RCTs) have explored the effect of unsupervised web-based or video-demonstrated individual exercise and education compared with conventional group-based PR in patients with stable moderate-to-severe COPD.^{13,14} The studies did not find differences between interventions for outcomes of walking capacity and respiratory symptoms.^{13,14}

One study including patients with COPD and comorbid heart failure (NYHA II-IV) compared home-monitored exercise and weekly individual telephone supervision with usual care (no intervention). The intervention provided clinically relevant differences in walking capacity, respiratory symptoms and QoL compared with usual care. Furthermore per-protocol analyses showed that the gains were maintained at the 2-month follow-up.¹⁵ Lastly, in patients with moderate COPD, one small RCT study (n=37) compared usual care (no intervention) with a supervised pulmonary tele-rehabilitation (PTR) programme in groups of two to four patients.¹⁶ This study showed significant and clinically relevant between-group difference on endurance shuttle walk, anxiety and depression symptoms and self-efficacy in favour of supervised PTR.¹⁶ All four studies are limited in their conclusions as none declared a priori-design (superior, equivalence, non-inferior) in the trial registry protocol, and just two studies stated a hypothesis.^{14,16} Although results from the recent PTR studies are promising, effects from supervised PTR in groups compared with conventional outpatient supervised PR in groups remain to be investigated. Consequently, evidence is needed to ascertain any possible effect of a fully supervised real-time PTR programme on relevant outcomes. To our knowledge, our study is the first RCT investigating the short-term and medium-term effect of a supervised PTR programme compared with a supervised conventional PR programme on walking capacity, symptoms, QoL and PAL in patients with COPD, $FEV_1 < 50\%$ and a high symptom burden eligible for routine hospital-based outpatient PR. We hypothesised that the supervised PTR programme would be superior to a supervised conventional PR regarding change in 6min walk distance (6MWD) because of an expected higher adherence rate, leading to a greater response.¹⁷

This paper reports on the clinical outcomes. A full economic analysis will be published separately.

METHODS

Trial design and participants

We conducted a randomised clinical, assessor-blinded and statistician-blinded, superiority, multicentre trial with two parallel groups to investigate the effect of supervised PTR compared with conventional PR on walking capacity in patients eligible for outpatient hospital-based PR. Patients were recruited from the respiratory departments of eight different university hospitals in Greater Copenhagen during March 2016 to October 2017. Inclusion and exclusion criteria corresponded to the criteria for outpatient hospital-based routine PR in the Capital Region of Copenhagen, Denmark, and pertained to adults with a clinical diagnosis of COPD defined as $FEV_1/FVC < 0.70$, $FEV_1 < 50\%$, Medical Research Council ≥ 2 and no participation in PR within 6 months of the start of intervention.^{17,18} All patients provided written and verbal informed consent.

Randomisation and blinding

After baseline assessments, patients were randomly allocated 1:1 to receive PTR or conventional hospital-based PR. The allocation followed a computer-generated randomisation list made by a biostatistician for each recruiting hospital; treatment was denoted as A and B to ensure blinding of the biostatistician. A senior manager from an independent research department was responsible for the randomisation list and provided the draw to ensure concealment. All assessors were blinded to group allocation, hypotheses and intervention details. Patients were not possible to blind for allocation. In the case of failure to keep the assessor blinded, a second assessor was available to conduct the blinded assessment on another day. The biostatistician had the main responsibility for the data analyses.

Intervention

Pulmonary tele-rehabilitation

The details and appropriate dosage set-up from both intervention programs are available in the online supplementary material and in our previously published protocol article.¹⁷ In brief, the PTR programme was designed by the study group and aligned with exercise intensities and education themes from conventional PR. It was a group-based, supervised and standardised programme performed by the patients in their homes three times weekly for 10 weeks via a videoconference software system installed on a single touch screen. The exercise sessions lasted 35min (weekly exercise volume 105min) with incorporated warm-up and high repetitive time-based muscle endurance training followed by 5min rest before beginning a patient education session of 20min (weekly education volume 60min).

Conventional pulmonary rehabilitation

The conventional outpatient hospital-based PR programme was group-based, supervised and standardised and was performed twice a week for 10 weeks (in one hospital, for 12 weeks). The programme followed the Danish Health Authority's National Clinical Guideline and the Regional Guidelines.^{17,19,20} The exercise sessions lasted 60min and incorporated warm-up, endurance and resistance training and a cool-down period (weekly exercise volume 120min). The patient education sessions lasted 60 to 90min and took place once a week after the exercise session (detailed online supplementary available).

Outcomes

Full details on outcome, assessment procedures and quality control are available in the online supplementary material. Briefly, the primary outcome was change in the 6MWD on completion of the programme. Secondary outcomes were COPD Assessment Test (CAT), Hospital Anxiety and Depression Scale (HADS), EuroQol 5-Dimension Questionnaire (EQ-5D), the 30s sit-to-stand test (30sec-STST), Clinical COPD Questionnaire (CCQ) and Physical Activity Level (PAL). The PAL was measured with activePAL triaxial accelerometer (PAL Technologies Ltd, Glasgow, UK) worn 24 hours for 5 days. PAL was measured on 73 patients residing within a radius of 25km of Bispebjerg University Hospital. All assessment procedures were performed at baseline, end of intervention and at 22 weeks' follow-up from baseline. The procedures were reproducible and have been published.²¹ Descriptive variables included body mass index, smoking status, medication and Charlson Comorbidity Index, spirometry and anthropometric measures, which followed the standardised protocols from the Danish Society of Respiratory Medicine.²² Adverse events, hospitalisations and deaths were recorded throughout the trial by the National Health Data Authorities.

Statistical analysis

For the 6MWD, a change of 26m is considered a minimal clinically important difference (MCID) in patients with COPD and $FEV_1 < 50\%$.^{23–25} Based on a two-sample independent t-test with an MCID of 26m, a SD of 44.6m,²⁴ a power of 80%, a significance level of 0.05 and an anticipated drop-out rate of 30%, 134 patients were recruited. Using this sample size, expected SD and existing MCID, power estimations for the secondary outcomes revealed 80% power to detect MCID in all secondary outcomes except CCQ and PAL.¹⁷

Descriptive data for the PTR and conventional PR are presented as mean and SD for continuous variables and frequency for categorical variables. Differences between the intervention groups in change of primary and secondary outcomes (end of intervention - baseline and 22 weeks' follow-up - baseline) were analysed by mixed effect models. The models included adjustment for treatment group, age, sex, body mass index, FEV_1 , Charlson Comorbidity Index, smoking status and a random effect for hospi-

tal allocation. To account for possible regression to the mean effect, the baseline measure for the outcome was also included as a fixed effect variable in the models. Normal distribution of the model residuals was evaluated by Q-Q plots. All data are considered missing at random, using this with the likelihood-estimation in the mixed effect model, the ignorability assumption for the likelihood estimator is used to account for missing data in the model estimates²⁶ (number of data sets is stated in tables 1 and 2 and online supplementary tables S2 and S3). Group differences on number of patients remaining in their programmes for the full intervention period, adherence, hospitalisation and death were analysed with χ^2 test. Adherence/attendance was defined as a patient participating in an entire scheduled exercise and education session. Analysis of age and sex differences between patients with and without outcome measures was done by χ^2 and Wilcoxon rank-sum test. Per-protocol analysis included patients attending $\geq 70\%$ of the planned sessions. Statistical analyses were carried out using R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). P values of less than 0.05 were considered statistically significant.

RESULTS

Recruitment

Of the patients suitable for hospital-based PR, 1099 met the inclusion criteria and were considered; 714 patients refused PR and were thus deemed ineligible. Of 385 eligible patients, the majority (n=251) wished to undertake conventional PR and declined participation in the study. One hundred and thirtyfour patients provided informed consent and were randomised (n=67 in each group) (figure 1). Baseline characteristics are shown in table 1.

Primary outcome

Tables 2 and 3 show the differences between and the changes within the groups at the end of PR/PTR and at the 22 weeks' follow-up from baseline. We found no statistically significant between-group difference for change in the 6MWD after intervention (table 2). Both groups demonstrated statistically significant improvements in the 6MWD after intervention, but the gain was sustained and significant only in the PTR group at 22 weeks' follow-up from baseline (table 3). None of the group improvements exceeded the MCID at any measurement time point.

Secondary outcomes

The between-group difference for changes in respiratory symptoms (CAT) was statistically different at the end of intervention with a greater symptom reduction difference of -1.6 points ($p=0.04$) in the PTR group that did not exceed the MCID (table 2). There was no between-group difference at the 22 weeks' follow-up from baseline. The groups did not exceed the MCID in respiratory symptom reduction at any measurement time point (table 3). The PTR group had a statistically significant reduction in anxiety and depression scores (HADS-A and HADS-D) compared with the conventional PR group after intervention, but it did not exceed the MCID. There were no between-group differences at the 22-week follow-up (table 2). The within group improvements on the anxiety domain were significant for the PTR group after intervention but did not exceed the MCID and the improvement was not sustained at the 22-week follow-up.

No group exceeded the MCID for QoL (EQ-5D-VAS) and lower limb muscle function (30sec-STS) (table 3). We registered a statistically significant decrease in number of daily steps per day in the PR group from baseline to end of intervention and to the 22-week follow-up, whereas daily steps per day remained unchanged in the PTR group (table 3). There was no difference between groups in the per-protocol analyses in any outcome at any measurement time point (see online supplementary tables S2 and S3).

Table 1 Baseline characteristics

Variables	All (N=134)	PTR (N=67)	PR (N=67)
Female sex, n (%)	74 (55)	35 (52)	39 (58)
Age, year	68.3 (9.0)	68.4 (8.7)	68.2 (9.4)
Body mass index, kg/m ²	25.7 (5.8)	25.5 (5.0)	25.9 (6.4)
FEV ₁ , % predicted	33.1 (9.4)	32.6 (10.3)	33.7 (8.4)
FEV ₁ /FVC, %	43.3 (11.2)	43.9 (11.3)	42.7 (11.1)
GOLD I/II/III/IV, %	0/0/61/39	0/0/55/45	0/0/67/33
A/B/C/D, %	2/34/4/60	5/34/3/58	0/33/4/63
LTOT, n (%)	20 (15)	11 (16)	9 (13)
SpO ₂ at rest, %	94.6 (2.8)	94.6 (2.4)	94.8 (3.1)
MRC 1/2/3/4/5, n	0/2/65/50/17	0/2/30/27/8	0/0/35/23/9
Smoking status, n (%)			
Never	3 (2)	2 (3)	1 (1)
Former	99 (75)	51 (79)	48 (72)
Current	30 (23)	12 (18)	18 (27)
Pack-year history, mean (SD)	43.5 (20.2)	42.4 (23.1)	44.5 (17.3)
BODE index points, median (IQR)	5.0 (4–6)	5.0 (4–7)	5.0 (4–6)
Charlson Comorbidity Index 1/2/ ≥ 3 , (%)	40/37/23	45/40/15	34/33/33
Exacerbations, previous 12 month, (median, IQR)	2 (0–3)	2 (0–4)	2 (1–3)
Current medication, n (%)			
SABA	112 (84)	56 (84)	56 (84)
SABA + SAMA	11 (8)	6 (9)	5 (7)
LABA	2 (1)	1 (1)	1 (1)
LAMA	3 (2)	2 (3)	1 (1)
LABA + LAMA	24 (18)	12 (18)	12 (18)
LABA + ICS	8 (6)	5 (7)	3 (5)
LABA + LAMA + ICS	93 (69)	45 (67)	48 (71)
Oral steroids	2 (1)	2 (3)	0 (0)
Walking aid, walker/other, n (%)	27/18 (34)	14/9 (34)	13/9 (33)
Highest 6MWD, metre	327.3 (102.8)	322.3 (108.3)	332.3 (97.5)
Highest 30sec-STS, repetitions	9.8 (4.3)	9.9 (4.7)	9.6 (3.8)
Physical activity level*			
Daily step count, steps	3091 (2161)	2779 (1966)	3422 (2335)
Time sedentary, min	1205 (133)	1244 (121)	1164 (134)
Time active, min	235 (133)	196 (121)	276 (134)
CAT, score	20.1 (7.0)	19.8 (7.3)	20.4 (6.6)
HADS, score			
HADS-anxiety	6.3 (3.5)	6.8 (3.8)	5.9 (3.1)
HADS-depression	4.3 (3.0)	4.5 (2.1)	4.1 (3.1)
EQ-5D, VAS score	52.7 (19.2)	51.5 (19.4)	53.9 (19.1)
EQ-5D, index score	0.68 (0.16)	0.66 (0.20)	0.70 (0.12)
CCQ, score			
Symptoms	2.9 (1.2)	2.8 (1.2)	3.0 (1.2)
Mental	2.9 (1.2)	2.8 (1.1)	3.0 (1.3)
Functional	2.8 (1.4)	2.8 (1.5)	2.9 (1.4)
Total	2.8 (0.9)	2.7 (0.9)	2.9 (1.0)

Data are presented as mean (SD) except where otherwise indicated.

*ActivePAL triaxial accelerometer worn by in total 73 patients (PTR/PR: 37/36). Any statistically significant difference between PTR and PR denoted * $p<0.05$.

A/B/C/D, risk stratification, airflow obstruction, dyspnea and exercise capacity; BODE index, body mass index; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; EQ-5D, Euro-QoL 5-dimension; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Score; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTOT, longterm oxygen therapy; MRC, Medical Research Council; 6MWD, 6 min walk distance; PR, pulmonary rehabilitation; PTR, pulmonary tele-rehabilitation; SABA, short-action β_2 -agonist; SAMA, short-acting muscarinic antagonist; 30-sec STS, 30 s sit-to-stand test; SpO₂, arterial oxygen saturation as measured by pulse oximetry; VAS, Visual Analogue Scale.

The attendance rate was a median of 25 session (IQR: 20 to 28) in the PTR group and 16 session (IQR: 8 to 19) in the PR group and thus the exercise volume was a median of 750min (IQR: 600 to 840) in the PTR group and 960min (IQR: 480 to 1140) in the PR group. A significantly higher number of patients remained in the PTR programme for the full intervention period compared with the PR programme (PTR: 57/67 vs PR: 43/67; OR: 3.18 (95% CI: 1.37 to 7.35), $p<0.01$). However, there was no difference between groups for those who attended $\geq 70\%$ of the programs' total sessions, (PTR: 49/67 vs PR: 42/67; OR: 1.68 (95% CI: 0.78 to 3.37), $p<0.27$). The mean adherence rate among drop-outs who attended at least one session was 50% of all sessions (IQR%:

Table 2 Between-group differences in primary and secondary outcomes in PTR and PR groups. Intention-to-treat principle

	Between-group differences from baseline			
	(95%CI) PR-PTR (unadjusted)		PR-PTR (adjusted)	
	End rehabilitation†	22 weeks from baseline‡	End rehabilitation†	22 weeks from baseline‡
Primary outcome				
6MWD, min	6.3 (−9.8 to 22.5)	−11.0 (−34.4 to 12.4)	8.3 (−7.7 to 24.3)	−3.9 (−27.9 to 19.9)
Secondary outcomes				
30sec-STs, reps	0.5 (−0.6 to 1.5)	0.4 (−0.7 to 1.4)	0.5 (−0.6 to 1.5)	0.5 (−0.6 to 1.6)
CAT, points	1.4 (−0.1 to 3.0)	−0.5 (−2.6 to 1.5)	1.6 (0.1 to 3.3)*	−0.2 (−2.1 to 1.8)
HADS				
Anxiety, points	1.1 (0.1 to 2.1)*	0.2 (−0.9 to 1.4)	1.2 (0.2 to 2.3)*	0.4 (−0.8 to 1.6)
Depression, points	0.7 (−0.1 to 1.5)	−0.2 (−1.3 to 1.0)	0.9 (0.1 to 1.7)*	−0.2 (−1.3 to 1.0)
EQ-5D-VAS, points	−0.2 (−6.4 to 5.9)	0.8 (−5.8 to 7.5)	−0.2 (−6.2 to 5.9)	1.6 (−5.1 to 8.3)
CCQ				
Function, points	0.1 (−0.2 to 0.5)	0.1 (−0.2 to 0.5)	0.1 (−0.2 to 0.5)	0.2 (−0.2 to 0.5)
Mental, points	0.1 (−0.3 to 0.6)	−0.1 (−0.4 to 0.3)	0.3 (−0.2 to 0.7)	0.1 (−0.3 to 0.5)
Symptoms, points	0.2 (−0.1 to 0.5)	0.1 (−0.3 to 0.5)	0.2 (−0.1 to 0.5)	0.1 (−0.2 to 0.5)
Total, points	0.2 (−0.1 to 0.4)	0.1 (−0.2 to 0.3)	0.2 (−0.1 to 0.5)	0.1 (−0.1 to 0.4)
PAL				
Steps per day	−283 (−845 to 278)	−302 (−1035 to 419)	−436 (−1010 to 138)	−103 (−886 to 597)
Sedentary, min	9.4 (−35.2 to 51.3)	8.6 (−53.8 to 36.6)	7.7 (−49.0 to 52.2)	14.6 (−32.5 to 58.5)
Active, min	−9.4 (−51.3 to 35.4)	−8.6 (−36.6 to 53.8)	−7.7 (−52.2 to 49.0)	−14.6 (−58.5 to 32.5)

Data are mean difference (95% CI).

*P value for group mean change differences <0.05.

†Complete observations (n) used for the likelihood estimate from end of rehabilitation to baseline (total): 6MWD: (115); 30sec-STs: (115); CAT: (119); HADS: (110); EQ-5d-VAS: (119); CCQ: (119); PAL: (59).

‡Complete observations (n) used for the likelihood estimate from 22 weeks' follow-up from baseline to baseline (total): 6MWD: (95); 30sec-STs: (95); CAT: (106); HADS: (100); EQ-5d-VAS: (104); CCQ: (106); PAL: (55).
CAT, COPD Assessment Test; CCQ, COPD Clinical Questionnaire; EQ-5D, EuroQol 5-Dimension Questionnaire; HADS, Hospital Anxiety and Depression Scale; 6MWD, 6 min walk distance; PAL, physical activity level; PR, pulmonary rehabilitation; PTR, pulmonary tele-rehabilitation; 30sec-STs, 30 s sit-to-stand test; VAS, Visual Analogue Scale.

42 to 64) in the PTR programme versus 33% of all sessions (IQR%: 18 to 49) in the PR programme.

Two drop-outs, both in the PR group, were potentially related to adverse effects of the PR programme. Both events were related to overload with subsequent pain in the knee and groin, respectively, and did not require medical treatment. In total, 41 hospital admissions related to COPD exacerbations were recorded (PTR: n=21; PR: n=20; p=0.77) during the rehabilitation period, and 74 hospitalisations related to COPD exacerbations (PTR: n=38; PR: n=36; p=0.97) were recorded at the 22-week follow-up (see the online supplementary S for diagnostic codes used in the registry from the National Health Data Authorities and online supplementary S5 for hospital days and outpatient visits). There was no significant difference between groups for all cause hospitalisations during rehabilitation. Three deaths (PTR: n=1; PR: n=2) occurred during the rehabilitation period, and another three had died at the 22-week follow-up (p=1.0).

No difference could be shown between patients with and without missing outcome measurement on sex, all p values >0.07. By contrast, the median age was significantly higher among patients with missing values for 6MWD, 30sec-STs, repetitions and CCQ mental score.

Registered problems with the technical solution

Tables 2 and 3 show the differences between and the changes within the groups at the end of PR/PTR and at the 22 weeks' follow-up group session (49/360). Individual patient cancellation caused by technical problems was 12 of 1902 individual connections.

DISCUSSION

The main finding of this multicentre, single-blinded, randomised clinical trial was that supervised PTR was not superior to conventional hospital-based PR regarding walking capacity (6MWD). More patients completed PTR than PR, whereas, contrary to our pre-hypothesis, there was no between-group difference in adherence rate (attending ≥70% of the planned sessions).

To our knowledge, the effects of a supervised PTR programme compared with a supervised conventional PR programme have not been previously investigated. Tsai *et al* found a clinically relevant effect on 6MWD and endurance shuttle walk test (ESWT) from supervised PTR compared with no intervention.¹⁶ The study by Bernocchi *et al*¹⁵ including patients with both COPD and heart failure reported superiority on 6MWD from an individual home-monitored exercise programme with a weekly phone call compared with no intervention; the intervention group exceeded the MCID and maintained the gain at the 2-month follow-up.¹⁵

The studies by Bourne *et al*¹³ and Chaplin *et al*¹⁴ compared the effect of unsupervised web-based or video-demonstrated individual exercise and education with conventional group PR and found comparable between-group effects on walking tests and within-group changes that exceeded the MCID for 6MWD and ESWT but not for incremental shuttle walk test.^{13 14}

By contrast, we found that neither conventional PR nor PTR improved the 6MWD above the MCID. Differences in population characteristics could in part explain our negative result. Compared with the above-mentioned studies, patients in our cohort had lower FEV₁, higher symptom burden, more exacerbations, lower walking capacity and most likely more locomotor disadvantages because in our study, 34% used a walking aid. Use of a walking aid or other indications of frailty have not been reported in the previous PTR studies.^{13–16} We recruited patients with identical real-world inclusion criteria for hospital-based PR, which could limit the consistency and efficacy of the results; however, our study reflects routine practice. Recently, two large RCTs by Holland *et al*²⁷ and Horton *et al*²⁸ including in total 453 patients with COPD, compared home-based PR with supervised centre-based PR, using a pragmatic trial design, also failed to achieve the expected MCID on walking capacity from both interventions. Finally, a retrospective cohort study of 2068 patients with COPD of differing severity and with different characteristics receiving gold standard outpatient or inpatient PR in the Netherlands reported that only 40% to 50% of all patients exceeded the MCID for 6MWD, HADS-A, HADS-D and St George's Respiratory Questionnaire, while the group average improvement

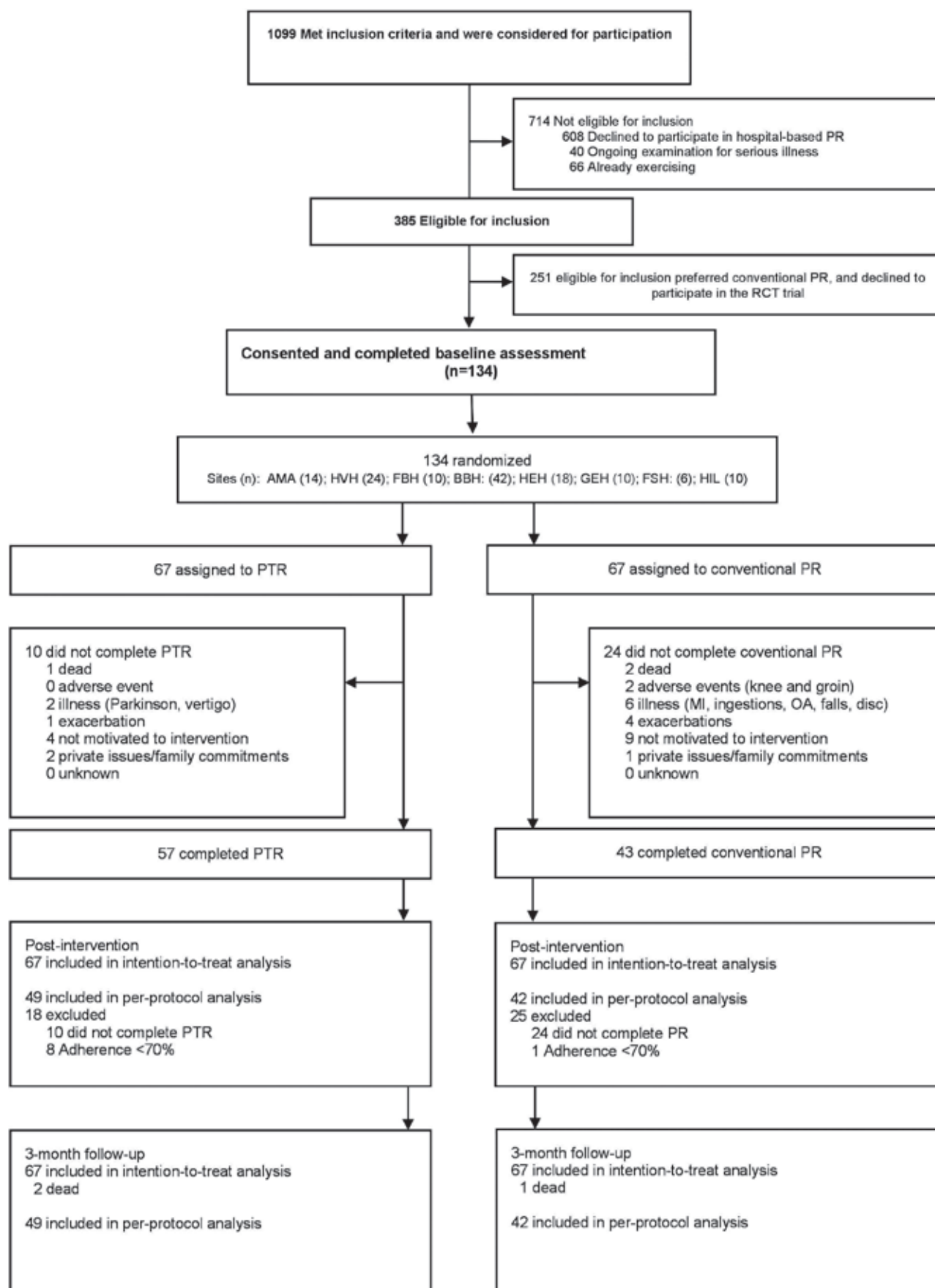


Figure 1 Estimated trajectories of FEV₁ (mL) decline by weight change profiles. The figure shows estimated FEV₁ values and their corresponding 95% CI. Models are adjusted for sex, height, age, age squared, smoking status, an interaction term between smoking status and age, current asthma and spirometer type. Reference category: normal BMI at baseline and stable weight during follow-up. All graphs are presented with a 'jitter' (0.05) to avoid overlap of CI bars. BMI, body mass index; FEV₁, forced expiratory volume in 1 s.

Table 3 Within-group changes in primary and secondary outcomes in PTR and PR groups. Intention-to-treat principle

	Within-group changes from baseline (95%CI)			
	PTR (n=67)		PR (n=67)	
	End rehabilitation†	22 weeks from baseline‡	End rehabilitation†	22 weeks from baseline‡
Primary outcome				
6MWD, min	17.2 (5.8 to 28.5)*	22.0 (5.0 to 39.1)*	23.5 (12.1 to 35.0)*	11.0 (−5.2 to 27.2)
Secondary outcomes				
30sec-STs, reps	1.3 (0.4 to 2.0)*	1.1 (0.1 to 2.0)*	1.7 (0.9 to 2.5)*	1.5 (0.5 to 2.3)*
CAT, points	−1.7 (−3.2 to −0.2)*	−0.5 (−1.9 to 1.1)	−0.3 (−1.8 to 1.2)	−1.0 (−2.5 to 0.6)
HADS				
Anxiety, points	−1.0 (−1.7 to −0.2)*	−0.5 (−1.4 to 0.5)	0.1 (−0.6 to 0.8)	−0.3 (−1.2 to 0.7)
Depression, points	−0.4 (−1.1 to 0.3)	0.5 (−0.4 to 1.5)	0.3 (−0.4 to 1.0)	0.3 (−0.6 to 1.4)
EQ-5D-VAS, points	3.2 (−1.2 to 7.6)	3.5 (−1.2 to 8.2)	2.9 (−1.4 to 7.2)	4.2 (−0.4 to 9.0)
CCQ				
Function, points	−0.3 (−0.5 to −0.1)*	0.1 (−0.1 to 0.4)	−0.1 (−0.4 to 0.1)	0.1 (−0.2 to 0.5)
Mental, points	−0.2 (−0.6 to 0.1)	−0.1 (−0.5 to 0.3)	−0.1 (−0.4 to 0.2)	−0.1 (−0.4 to 0.3)
Symptoms, points	−0.3 (−0.6 to −0.1)*	−0.2 (−0.5 to 0.1)	−0.2 (−0.4 to 0.1)	0.1 (−0.3 to 0.5)
Total, points	−0.3 (−0.4 to −0.1)*	0.0 (−0.2 to 0.2)	−0.1 (−0.3 to 0.1)	0.1 (−0.2 to 0.3)
PAL				
Steps per day	−116 (−503 to 270)	−292 (−852 to 307)	−400 (−803 to −2.3)*	−594 (−1164 to −57)*
Sedentary, min	29.0 (−29.9 to 95.4)	18.8 (−11.8 to 49.3)	38.3 (−21.7 to 107.3)	10.1 (−21.0 to 41.3)
Active, min	−29.0 (−95.4 to 29.9)	−18.8 (−49.3 to 11.8)	−38.3 (−107.3 to 21.7)	−10.1 (−41.3 to 21.0)

Data are mean difference (95% CI). Estimates adjusted for baseline outcome measure. Estimates calculated for baseline measure equal to the mean baseline measure for study population.

*P value within group changes <0.05.

†Complete observations (n) used for the likelihood estimate from end of rehabilitation to baseline (PTR/PR): 6MWD: (56/59); 30-sec STs: (56/59); CAT: (59/62); HADS: (53/57); EQ5d-VAS: (57/62); CCQ: (57/62); PAL: (30/29).

‡Complete observations (n) used for the likelihood estimate from 22 weeks' follow-up from baseline to baseline (PTR/PR): 6MWD: (44/51); 30sec-STs: (44/51); CAT: (53/53); HADS: (50/50); EQ5d-VAS: (51/53); CCQ: (53/53); PAL: (28/27).

CAT, COPD Assessment Test; CCQ, COPD Clinical Questionnaire; EQ-5D, EuroQol 5-Dimension Questionnaire; HADS, Hospital Anxiety and Depression Scale; 6MWD, 6 min walk distance; PAL, physical activity level; PR, pulmonary rehabilitation; PTR, pulmonary tele-rehabilitation; 30sec-STs, 30 s sit-to-stand test; VAS, Visual Analogue Scale.

almost exceeded the MCID.²⁹ In this study, Spruit and colleagues demonstrated that patients respond very heterogeneously on both the physical and self-reported clinical outcomes. This suggests the need for reconsideration of the assumption that all patients with COPD are likely to respond similarly and sufficiently to specific and restricted primary outcomes in either conventional PR programs²⁹ or alternative home-based programs.^{27 28}

From the Cochrane review it appears that 43% of the larger studies (including more than 30 participants in each group) did not exceed the MCID for the 6MWD1 and, importantly, meta-epidemiological studies have shown that single-centre trials yield 14% to 27% larger effect sizes than do multicentre trials even when analyses are adjusted for sample size and bias.³⁰

The completion rate in our study was significantly higher in the PTR group than in the PR group; however, we did not find a significant higher adherence rate in the PTR group (73%) compared with the PR group (62%). The drop-out rate of 36% in the PR group was anticipated and comparable to other studies reporting drop-out rates from 10% to 50%.^{6 7 11 27 28 31} The annual 2018 data audit from the Danish Regional Quality Database in COPD revealed that 45% of all participants in Danish outpatient hospital PR adhere to less than 50% of the PR program.³² The real-world data from this quality database reflect the challenges with adherence in a conventional hospital-based real-world PR programme and should be contrasted with the distinctly higher adherence in the PTR programme, where 73% of patients attended ≥70% of the sessions. Thus, PTR seemingly has the potential to overcome some barriers to adherence and completion. It should be noted that only one-third of patients eligible for this study were willing to participate in this RCT as they stated 'preferring conventional PR', thus limiting the external validity (figure 1). Patient preferences and motivation have a potential impact on the outcomes achieved in different settings. This indicates that PTR could be an alternative for some patients eligible for outpatient hospital-based PR. As the 134 patients who agreed to participate may be particularly motivated, the 608 patients who declined participation in conventional PR would be an important group of interest for

future research in the field of exploring the relevance and effects of PTR as an alternative delivery model.

There were also a number of important secondary findings in the present study. We investigated a cohort of patients with an extremely low level of physical activity, with average steps per day corresponding to basal and limited activity, for example, getting out of bed, making a meal and infrequent walks outside the home. This low and unchanged PAL throughout the study could affect the outcome and explain why the MCID in 6MWD was not exceeded since PAL and steps above 7500 per day are considered essential for physical functioning and overall health.³³

We found that the PTR group had a significant reduction in CAT, anxiety and depression scores (HADS-A and HADS-D) compared with the PR group after intervention; however, the reduction did not exceed the MCID and the difference was not persistent at the 22-week follow-up. The higher completion rate in the PTR group, where patients continued to receive realtime attention and care, could be a plausible explanation of the differences after intervention. The previously mentioned PTR studies by Chaplin *et al*¹⁴ and Bourne *et al*¹³ did not find any between-group differences in HADS after intervention, while Tsai *et al*¹⁶ found differences identical to ours with supervised PTR compared with no intervention. The impact of real-time supervision versus the web-based PTR, including the means of communication, is not possible to quantify but could potentially explain some of these inconsistent findings between the PTR studies.

We are not aware of any studies comparing non-supervised PTR with supervised PTR. Ability to navigate and interact independently on a tablet and a webpage was required in the non-supervised PTR studies, whereas for the patients in our study, it was sufficient to have naive technical ability and skills.^{13 14 17}

Essentially, future tele-rehabilitation designs must include specific considerations regarding delivery form and content and technical skills of the targeted population, particularly if PTR is to be considered as an extended offer specifically to those who live remotely and to those who lack energy and resources to join a conventional PR programme.

The strengths of this study include the multicentre design, rigorous methodology, powering for an adequate sample size to test our a priori hypothesis and the intention-to-treat analysis, which limits the risk of bias. We recruited patients with severely progressed COPD using national inclusion and exclusion criteria identical to routine clinical practice for conventional outpatient hospital-based PR. Blinding was also a strength of the present study. Our assessment of outcomes was performed with documented small and acceptable measurement errors.²¹ A limitation of the study concerns the small but real variation in exercise content and volume among the seven hospitals delivering conventional PR, which was not possible to monitor and align. However, this is a true reflection of the real-world setting and thereby a real-world comparison. Different practical challenges to modelling, staffing and structuring PTR and differing patient acceptance of PTR in different countries, geographical regions and different types of healthcare system are limitations of the generalisability of our findings.

Proper organisation of PTR remains a challenge. It is a delicate balance in terms of decision-makers not limiting access to outpatient conventional PR and replacing it with PTR to save the costs related to buildings, equipment, transportation, etc, while endeavouring to provide an option for patients who are unable to attend the outpatient programme. From our perspective, many research questions remain unanswered regarding PTR. Future research should address subjects such as which patients are best suited to PTR and how we accommodate the increasing focus on personalised training. We need to find ways to enhance digital literacy among elderly, frail patients and discover whether the supervised or web-based tele-model is more effective as well as cost-effective. Furthermore, it is not yet known if applications will be as good as online groups with videoconferencing.

Other aspects include the role of monitoring PTR and the long-term health-related and QoL-related outcomes. Another issue regarding future studies of both PR and PTR concerns the measured outcomes of interest. As results to date regarding the traditional exercise and QoL outcomes are not convincing in patients with severe disease status, it is necessary to try a different approach. Outcomes that embrace activities of daily living and/or reduce symptoms such as dyspnoea and fatigue are warranted. In the study by Spruit *et al*²⁹ a composite endpoint for response to a 40-session PR programme was constructed and patients were clustered according to response profile. Interestingly, those in the 'very good responder' cluster were characterised by a worse baseline health status in comparison with the other clusters. However, it was unclear whether this multidimensional response was driven by a single outcome measure or several measures, thus calling for further research in the context of composite outcomes.

CONCLUSION

In conclusion, supervised PTR was not superior to supervised conventional PR in increasing 6MWD. Improvements in completion of PTR compared with PR were found; however, future non-inferiority studies of the 6MWD for PTR and PR are needed to justify recommending PTR based on better adherence to the programme.

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Data availability statement Data are available upon reasonable request.

Data sharing plan: supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial. (1) Will individual, de-identified participant data (including data dictionaries) be shared? Yes. (2) What data in particular will be shared? Participant data that underlie the results reported in this article, after de-identification (text, tables, figures and appendices). (3) Whether additional, related documents will be made available? Published study protocol, statistical analytics coding used in r, consent form (in Danish). (4) When and for how long the data will become/be available? Data available until 31 December 2021. (5) The criteria to access the data (including who can request access and for what types of analyses, and the name of the data repository). Proposal for data use should be addressed to henrik.hansen.09@regionh.dk. Data access in Denmark are under very strict juristic data protection law. any possible access or sharing demands a part application to; (1) Danish Data Protection agency, (2) ethics committee of the capital region, (3) national health Data authorities. Only if the applications are approved data will be considered available for sharing. The authors will not be able to support this process and a prolonged process must be expected. **Open access** This is an open access article distributed in accordance with the creative commons attribution non commercial (cc BY-nc 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. see: <http://creativecommons.org/licenses/by-nc/4.0/>.

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Caracterização do microbioma da expetoração na DPOC: para além da deteção de patógenos singulares

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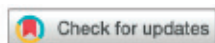
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RESUMO

Técnicas de sequenciamento microbiano independentes da cultura têm revelado que o trato respiratório alberga um microbioma complexo não detetável por métodos de cultura convencionais. O contributo do microbioma para a biopatologia da doença pulmonar obstrutiva crónica (DPOC) e o potencial para biomarcadores clínicos baseados no microbioma na DPOC ainda se encontram em fases precoces de investigação. A expetoração é uma amostra de fácil colheita e tem fornecido informação valiosa sobre a biopatologia da DPOC, tornando-se um tipo de amostra preferencial em estudos de microbioma. Embora seja provável que o microbioma da expetoração apenas reflita o microbioma respiratório de modo parcial, observam-se cada vez mais evidências de que a estrutura comunitária e diversidade microbianas estão associadas à gravidade da doença e aos resultados clínicos, tanto na DPOC estável como durante as agudizações. As evidências atuais têm estado, sobretudo, limitadas a estudos transversais com recurso ao sequenciamento genético de ARNr 16S, na tentativa de responder à questão “quem é?”. De modo a responder a questões em aberto, incluindo as diferenças entre técnicas de amostragem de expetoração, é necessário realizar estudos longitudinais com recurso a protocolos normalizados. Adicionalmente, com o avançar das tecnologias, os estudos de microbioma estão a ir além do exame do gene ARNr 16S de modo a incluir o sequenciamento total do metagenoma e do metatranscriptoma, assim como a caracterização do metaboloma. Apesar de ser tecnicamente mais difícil, a caracterização total do genoma e a metabolómica podem responder às questões “o que podem fazer?” e “o que estão a fazer?”. Esta revisão proporciona uma visão geral dos princípios básicos das técnicas de sequenciamento do microbioma de alto rendimento, a literatura atual sobre caracterização do microbioma da expetoração na DPOC e uma discussão das limitações associadas e perspetivas futuras.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent respiratory disease and the leading cause of morbidity and mortality worldwide.^{1,2} It is heterogeneous, but many patients experience progressive airflow obstruction, exacerbations and/or persistent symptoms of dyspnoea, cough and sputum production.² Exacerbations are heterogeneous and vaguely defined as acute worsening of respiratory symptoms outside of normal day-to-day variation, usually associated with a healthcare utilisation event (eg, prescription of oral steroids and/or antibiotics, emergency room visit). They are associated with accelerated disease progression, increased mortality and major healthcare costs.^{2–4} The heterogeneity of COPD overall, and exacerbations, in particular, complicates the clinical assessment of disease

severity and outcome. Determining the fundamental biology underlying COPD heterogeneity is vitally important, as is the identification of biomarkers to guide personalisation of therapeutic strategies.^{5–7}

Elucidating the role of respiratory microbiota with respect to COPD pathobiology has potential implications for improving diagnostics and predicting outcomes.^{8–12} The respiratory microbiome, which may be assayed using culture-independent microbial sequencing, is characterised by the micro-organisms and their genomes present in the respiratory tract under specific environmental conditions (eg, exposures or disease states).¹³ Metrics assessing respiratory microbiome composition differ between healthy controls and COPD, and alterations in bacterial abundance and microbial diversity (ie, microbes present in differing proportions) correlate with altered airway inflammatory processes.^{14–17}

Current knowledge of the respiratory microbiome still relies mainly on the 16S rRNA gene sequencing approach. Other high-throughput techniques, such as metagenomics, metatranscriptomics and metabolomics, will aid in both a broader investigation of microbial genomes and the examination of associated functional aspects. In this review, we provide an overview of the basic principles of high-throughput techniques for microbiome assessment and analytical approaches. Further, we discuss the current evidence, limitations and future perspectives of sputum microbiome profiling in COPD.

Basic principles of high-throughput sequencing techniques: 16S rRNA gene sequencing, shotgun metagenomics, metatranscriptomics, metabolomics

Culture-independent high-throughput sequencing techniques have revealed that the human body harbours a microbiome with a complexity far beyond the scope that is detectable by conventional culturing methods.^{18,19} Importantly, cultivation efforts can be extended in order to increase the detection rate of microbes, which represents a significant benchmark for evaluating new culture-independent sequencing technologies.²⁰ The choice of technique for microbiome assessment and characterisation should be based on the research question, with consideration of the strengths and weaknesses of each technique. The respiratory tract, certainly in stable COPD, is a low-biomass environment in which the microbial density decreases in a gradient from the upper (URT) to lower respiratory tract (LRT), where microaspiration from the URT is considered to be the dominant source.²¹

Therefore, microbial signals must be discerned from possible contamination during the sample collection and processing prior to analysis.^{22–23} Furthermore, appropriate sample collection and processing following standardised protocols, with particular attention to DNA and RNA extraction methods, should be followed as multiple steps in this process can influence microbe yield and diversity.²⁴ A comprehensive discussion of best practices for microbiome analysis overall and with respect to the respiratory tract have been well described previously.^{22–23–25–26} 16S rRNA gene sequencing was used in the pioneering work in respiratory microbiome research, and current knowledge still relies mainly on this approach.^{8–27} 16S rRNA sequencing is based on PCR amplification using primers that target the 16S ribosomal gene variable regions of bacterial genomes, which can be used for taxonomic classification.²⁸ This approach is rapid, well tested and relatively low cost. By focusing on a specific region of the bacterial genome, it requires only a limited sequencing depth. 16S rRNA sequencing is used to survey microbial communities, answering the question ‘who is there?’

There are many techniques for analysing microbial communities present within and across samples, but alpha and beta diversity are two of the most common metrics. Alpha diversity captures the number of operational taxonomic units (OTUs) present in a sample (‘richness’) and how they are distributed (‘evenness’), reducing the complexity of these relationships into a single metric. Commonly used alpha diversity metrics include the Shannon index or Simpson index.^{26–29} Beta diversity compares the dissimilarity between samples and provides a matrix of distance. Alpha and beta diversity do not, however, capture the full complexity and dimensionality of microbial community relationships. Thus, more recent work has begun to explore the microbiome in the context of microbial community ecology.³⁰ Community ecology theory provides a framework and set of analytical tools to consider how microbes interact with each other and their human host over time and space and in response to exposures or insults (eg, disease states). Newer sequencing approaches that capture microbial function and presence are poised to contribute greatly to our understanding of these ecological dynamics.

16S rRNA gene sequencing exhibits other important shortcomings that may be overcome by newer technologies. For example, it cannot distinguish between live and dead microbes, which may be relevant for several reasons, such as assessing the impact of antibiotic therapy in clinical samples.³¹ Also, 16S rRNA gene sequences are relatively short. Thus, closely related bacteria may share similar sequences, making a separation between different species challenging.²⁶ Finally, 16S sequencing analyses are restricted to the detection of bacteria and archaea since viruses or fungi do not carry 16S rRNA genes.

Shotgun metagenomic sequencing is based on unrestricted DNA sequencing of genetic content in a sample. This approach can capture DNA-based viruses and eukaryotic DNA, including fungal microorganisms, in addition to bacteria.²⁶ Shotgun metagenomics allows for an unbiased and deeper taxonomical analysis of the microbiome than 16S rRNA gene method, since dissimilar regions of microbial genomes are sequenced. The assembly of short sequencing reads into larger fragments can increase the discriminatory power between microbes, enhancing taxonomic resolution up to the species or strain level.^{25–32} Feigelman *et al* demonstrated how unbiased DNA sequencing in sputum from patients with cystic fibrosis (CF) can enhance in-depth microbiome profiling.³³ Furthermore, shotgun metagenomic analyses add insight into the question ‘what can these microbes do?’ The potential metabolic capacity of the microbiome can be evaluated by assigning microbial genes to pathway profiles and investigating potential cross-talk between the microbiome and human host and between microbes.^{34–35}

Metagenomic sequencing has several weaknesses. As with 16S rRNA gene sequencing, it is unable to distinguish between live and dead microbes. The high sequencing depths necessary for taxonomic classification may be prohibitively expensive, although these costs are diminishing.^{25–26} Most respiratory viruses are RNA-based and therefore not detectable by metagenomic approaches. Additionally, pathway profiling of microbial genes will only allow for the evaluation of potential metabolic capacities, and can thus only conjecture at functional roles.

Metatranscriptomic sequencing examines RNA-level genetic content. RNA sequencing (RNA-seq) provides a survey of microbiota that include RNA-based respiratory viruses.^{36–38} Unlike DNA-based methods, metatranscriptomics focuses on living microbiota. By assessing gene expression (transcriptome) of the microbiota, it can enable a better assessment of microbial functional activity. Further, this approach allows for a simultaneous assessment of the host transcriptome. Thus, metatranscriptomics may provide broader insight into the question ‘what are they doing?’ than metagenomics by allowing for an assessment of functional interactions between different microbiota and between host and microbes.

There are drawbacks to metatranscriptomics as well.³⁹ RNA is vulnerable with a short half-life and requires careful collection and storage associated with high costs. Further, results can be biased towards microbial genes with higher transcription rates. Consequently, it is preferable that RNA-based approaches are complemented by DNA-based sequencing so that RNA/DNA ratios and microbial transcriptional activity may be examined. Finally, the application of RNA-seq to microbiome research is still relatively new, especially with respect to the respiratory tract. Therefore, best practices for sample processing and analysis are still evolving.

Metabolomic data generation is based on chromatography techniques and detection methods, such as mass spectrometry or nuclear magnetic resonance, instead of sequencing.⁴⁰ Application of these technologies to microbiome research is still in its infancy and has been better studied in the gut than the respiratory tract. However, the techniques provide an opportunity to more accurately answer the question ‘what are the microbes doing?’ when used in combination with microbial and host sequencing that identify relevant alterations in microbial communities and host response. Microbial-derived metabolites include those synthesised directly by microbes and those produced by the host and biochemically modified by microbes.⁴¹ They are known to affect host physiology (host–microbiota interactions) as well as dynamics within the microbiome (microbe–microbe interactions). They have been shown to play important roles in health and disease. These include crucial roles in the maintenance of the epithelium and immune cell function, processes dysregulated in COPD pathogenesis.^{41–42} Thus, metabolomics-based analyses provide a promising opportunity for studying microbial–host dynamics within the respiratory tract.

Overall, evolving high-throughput methods are revolutionising microbiome research. Although 16S rRNA gene sequencing is still the most common technology used in respiratory microbiome research, shotgun metagenomics, metatranscriptomics and metabolomics are increasingly applied to microbiome background, however, its effect on an unbiased microbiome detection remains unknown.^{22–43} Further, standardisation of methods, including sample collection, processing and analytical pipelines, is required in order to further elucidate their utility in respiratory microbiome research.

Sputum microbiome profiling in COPD: the current body of evidence

The respiratory tract is an anatomically and physiologically complex organ. Physiological parameters, such as pH level,

relative humidity or temperature, change along the respiratory tract, creating niche-specific growth conditions for microbes.⁴⁴ Consequently, it is likely that the microbiome varies along the respiratory tract. Furthermore, airway microbiome profiles depend on sampling method (eg, nasal brushing, induced or expectorate sputum, bronchoalveolar lavage (BAL), epithelial brushing, bronchial biopsies) consistent with this niche specificity.^{17 45–47}

To exploit respiratory microbiome characteristics for COPD diagnostics, phenotyping and outcome prediction, it is necessary to identify microbiome biomarkers that are easily obtainable in a patient-friendly manner. Sputum closely aligns with these characteristics, making it a preferred sampling technique. Sputum microbiome characteristics, such as microbial diversity or relative abundance, are associated with disease severity and outcomes in stable COPD and exacerbations (see online supplementary table 1).^{10 11 45 48 49}

Sputum microbiome profiles in stable COPD

In stable COPD, reduced sputum bacterial microbiome diversity has been shown to be associated with more severe airflow obstruction.^{17 45 49 50} Galiana *et al* found that participants with severe airflow obstruction exhibited lower alpha diversity and a higher bacterial load in sputum samples, compared with participants with mild or moderate airflow obstruction.⁴⁹ This finding has since been reproduced in both sputum and BAL sampling.^{17 50 51}

These studies also reported a shift in the microbial flora with decreasing lung function towards potentially pathogenic bacterial genera, particularly those belonging to the gamma-proteobacteria class (eg, *Pseudomonas* or *Haemophilus spp*). Thus, the observed decrease in microbial diversity appears to be associated with their outgrowth. Although reduced microbial diversity has been identified at other mucosal sites (eg, gastrointestinal tract) in association with chronic inflammatory diseases (eg, inflammatory bowel disease), it remains of interest whether these associations are influenced by therapeutic interventions.⁵² Further, identifying causal relationships between chronic inflammation and microbial community changes is an active area of research.

The association between bacterial load and features of stable COPD appears to be complex and affected by chosen therapies.^{49 53} Garcha *et al* showed that higher bacterial load of potential pathogens, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, correlated with more severe airflow limitation in stable COPD.⁵³ Further, they reported a positive correlation between bacterial load and inhaled corticosteroids (ICS) dosage. In a randomised controlled trial, Brill *et al* reported that chronic antibiotic therapy, often used as an exacerbation preventative therapy, was associated with a ≥ 3 fold increase in antibiotic resistance among airway bacteria without decreasing the total bacterial load in sputum.⁵⁴ These associations between therapies and microbial load or function suggest that therapies regularly used in COPD management may have unintended consequences on the microbiome, although the significance of these consequences is unclear.

There is preliminary evidence that sputum microbial communities from COPD patients with more severe airflow obstruction may have shifted such that they lack potentially commensal bacteria, favouring more pathogenic microbes.⁴⁹ Several studies identified potential commensal bacteria in the URT, including *Dolosigranulum spp* and *Corynebacterium spp*, which appear to be associated with respiratory health and pathogen clearance.^{55–57}

Galiana *et al* found that the potentially commensal bacterial genus *Actinomyces* was less frequently recovered in sputum from patients with COPD with severe compared

with moderate airflow obstruction.⁴⁹ Iwase *et al* showed that commensal respiratory bacteria can directly suppress the outgrowth of potential pathogens belonging to the same genus or family, highlighting the importance of microbe–microbe interactions in maintaining homeostasis.⁵⁸ Potential new therapeutic approaches might not only aim at reducing colonisation of pathogenic microbes but also at increasing colonisation of commensal bacteria in the respiratory tract.

Sputum microbiome profiles in COPD exacerbations

GOLD guidelines recommend performing sputum cultures in patients with frequent exacerbations, severe airflow limitation and/or those requiring mechanical ventilation.² While the goal of sputum culture in this setting is to determine the presence of bacterial pathogens and to guide antibiotic treatment, culture is very limited in this role.^{59–61}

Evaluating the sputum microbiome with modern highthroughput sequencing technologies might contribute to enhanced exacerbation precipitant diagnosis. Sputum microbiome profiles have been shown to exhibit dynamic changes between stable COPD and exacerbations in at least a patient subset, involving the outgrowth of pathogens, decreased microbial diversity and increased abundance of pathogenic bacterial communities.^{11 62} There is also evidence that bacterial outgrowth, as occurs in overt infection, may not be necessary for bacteria to trigger an exacerbation. Strain shifts towards more pathogenic bacterial strains, without an overall change in bacterial abundance, have been identified as potential precipitants for some exacerbations.⁶³

Host biomarkers and microbial profiling in sputum samples suggest that at least three exacerbation subtypes exist, defined by both the airway inflammatory state and the suspected exacerbation precipitant: bacterial, viral and eosinophilic.¹⁰ Ghebre *et al* found that sputum samples clustered by exacerbation subtype exhibited differing microbial community characteristics.¹⁰ Exacerbations categorised as bacteria associated had the greatest

Proteobacteria abundance and a high *Proteobacterial Firmicutes* ratio in their sputum, while exacerbations categorised as eosinophilic exhibited greater sputum microbial alpha diversity.¹⁰ Mayhew *et al* found that exacerbations classified as bacterial and eosinophilic were more like to be repeated within a subject over time than viral exacerbations.⁵¹ Thus, exacerbations exhibit substantial biological heterogeneity. Considering exacerbations within the subtyping framework may add considerably to our understanding of underlying mechanisms and provide insight into more appropriate precision-guided management. Although changes in bacterial community structure appear to occur in only an exacerbation subset, dysbiosis is indeed associated with particular exacerbation features and worse outcomes.

Wang *et al* found that the sputum microbial community composition changes significantly from stable to exacerbation state in only ~40% of their cohort.⁴⁸ Participants with microbial dysbiosis had worse health status and lung function, particularly if research in other compartments (eg, gastrointestinal tract). A crucial challenge remains the depletion of host DNA, which represents the vast majority of DNA present in low-biomass samples.²² Samples can be pretreated to reduce the host genome they also had evidence of eosinophilic inflammation. Furthermore, the abundance of *Moraxella spp* increased in this study, corroborating other reports that find specific pathogenic phyla and genera are enriched in the exacerbation microbiome.^{11 62}

Leitao Filho *et al* found that reduced sputum microbial alpha diversity and altered beta diversity during hospitalised exacerbations were associated with increased 1-year mortality.⁶⁴ Interestingly, associations between limited diversity and

disease progression has also been described in other lung diseases, such as CF.⁶⁵ Together, these results indicate that the heterogeneous contribution of microbes to exacerbations may be clinically relevant.

Several reports have speculated that the contribution of typically non-pathogenic bacteria to alterations in microbial community ecology may be crucial to exacerbation pathogenesis. Wang *et al* identified an outgrowth of non-pathogenic *Proteobacteria*, in addition to pathogenic microbiota, during exacerbations. They speculate that this state of dysbiosis, with differing microbe–microbe and microbe–host interactions, leads to a dysregulated host inflammatory response.^{11 66} Huang *et al* reported a positive relationship between the abundance of COPD-associated pathogens during an exacerbation, (eg, *H. influenzae*, *Pseudomonas aeruginosa* or *Moraxella catarrhalis*) and phylogenetically related non-pathogenic bacteria.⁶² Leitaó Filho *et al* speculate that the absence of potentially commensal bacterial genera in the sputum microbiome is associated with clinical outcomes in exacerbations.⁶⁴ They found that both the presence of *Staphylococcus spp* (potentially pathogenic) and the absence of *Veillonella spp* (potentially commensal) in sputum were strongly associated with the increased risk of mortality after 1 year. This work highlights the need for a better understanding of the role of both pathogenic and commensal microbes within the respiratory microbiome during exacerbations.

Importantly, two studies did not find changes in diversity metrics between disease stability and exacerbations.^{51 67} Millares *et al* additionally failed to identify changes in bacterial abundance but did report changes in functional metabolic pathways of the microbiome during exacerbations. Mayhew *et al* did not identify a change in diversity metrics but did find an increase in the relative abundance of *Moraxella spp* during exacerbations.^{51 67} These reports provide further evidence of the overall phenotypic heterogeneity in exacerbations, but also emphasise the potential importance of strain shifts without changes in species or class-level microbial community structure in precipitating bacterial exacerbations. Standardised follow-up studies are required to validate current findings. Eventually, causation and mechanisms between sputum microbial community structure and host inflammatory response require further investigation, which demands causal models and rigorous methods.^{68 69} A promising approach was recently published by Sanna *et al*, using a bidirectional Mendelian randomisation analysis to assess causality between the gut microbiome and metabolic diseases.⁷⁰

Sputum microbiome profiles after therapeutic interventions of exacerbations

Current knowledge about the impact of empirical approaches to the treatment of exacerbations on sputum microbiome profiles is still scarce. Wang *et al* reported that steroid treatment alone was associated with reduced alpha diversity, increased abundance of *Proteobacteria* (including *Haemophilus* and *Moraxella spp*) and an increased *Proteobacteria:Firmicutes* ratio, whereas opposite trends were found in exacerbations treated with antibiotics (with or without steroids).¹¹ Huang *et al* also reported an enrichment of *Proteobacteria*, in addition to other bacterial phyla with steroid treatment, indicating that this treatment alone might increase the burden of specific microbiota.⁶² In the same study, antibiotic treatment had suppressive effects on this bacterial burden. In contrast to Wang *et al* findings, Huang *et al* observed a trend towards increased microbial diversity after steroid treatment and decreased diversity following antibiotic treatment.

Further research is needed to better understand treatment effects on respiratory microbial dynamics over time as well as microbial–host interactions. Segal *et al* took a promising

approach to study the antimicrobial effects of azithromycin in COPD.⁷¹ Using a combination of 16S sequencing and metabolomics they found decreased alpha diversity in azithromycin-treated BAL samples and increased bacteria-produced metabolites known to influence the host inflammatory response. More multi-omic studies integrating microbial and host data are needed to elucidate and characterise the potentially deleterious impact of chronic therapies in COPD to better guide therapy decisions.

In summary, the current body of evidence indicates that the severity of COPD is inversely correlated with sputum microbial diversity and is associated with an outgrowth of potentially pathogenic bacteria. Exacerbation subtypes exhibit altered sputum microbial community characteristics, providing potential targets for precision-guided management. Further studies, integrating microbial and host information, are needed to understand the impact of therapeutic interventions on the microbiome and interactions with the host. Eventually, potential new therapeutic approaches might not only aim at reducing the colonisation of pathogenic microbes but also to either increase the colonisation of commensal bacteria or modulate the associated host response.

Sputum microbiome profiling in COPD: limitations, challenges and future perspectives

There are several limitations of sputum microbiome profiling as well as challenges that should be addressed in future studies to better assess the utility of the technique in COPD microbiome research (figure 1):

Limitations and challenges: the biogeography of sputum

LRT sampling methods, such as BAL and bronchial biopsies or brushings, are invasive approaches and thus poorly suited for longitudinal assessment. However, COPD is generally a disease of the LRT. Thus, understanding the similarities and differences between these LRT sampling methods and more easily obtainable sputum sampling is essential for interpretation.^{47 72} In a small study (n=20), Sulaiman *et al* found that induced sputum microbiota were more similar to those obtained by oral wash than those obtained from the lower airway (bronchial biopsies) in participants with and without non-tuberculous mycobacterial infections.⁷² Durack *et al* also reported an enrichment of oral bacteria in induced sputum samples compared with bronchial biopsies.⁴⁷ However, they found that the abundance of genera identified in bronchial biopsies correlated quite well with those detected in both induced sputum and oral wash. Thus, despite the overall difference in microbial composition between URT and LRT sampling, sputum does have utility in assessing LRT microbiome composition, in particular, relative microbial abundance. These correlations between lower and upper airway microbe abundance underscore the theory that microaspiration of microbes from the URT is the primary source of bronchial microbiota.^{21 46,73} While characterising the airway microbiome using sputum should be done considering the limitations, the considerable strengths in comparison to LRT sampling should be considered as well. Sputum is easily obtainable and alterations in the sputum microbiome correlate with clinical outcomes. Thus, sputum microbiome biomarkers may be useful even if they do not accurately reflect the LRT microbiome.

Limitations and challenges: induced versus spontaneously expectorated sputum

Differences in microbiome profiles obtained from spontaneous versus induced sputum samples are particularly understudied. Although patients without spontaneous sputum production can safely undergo sputum induction even

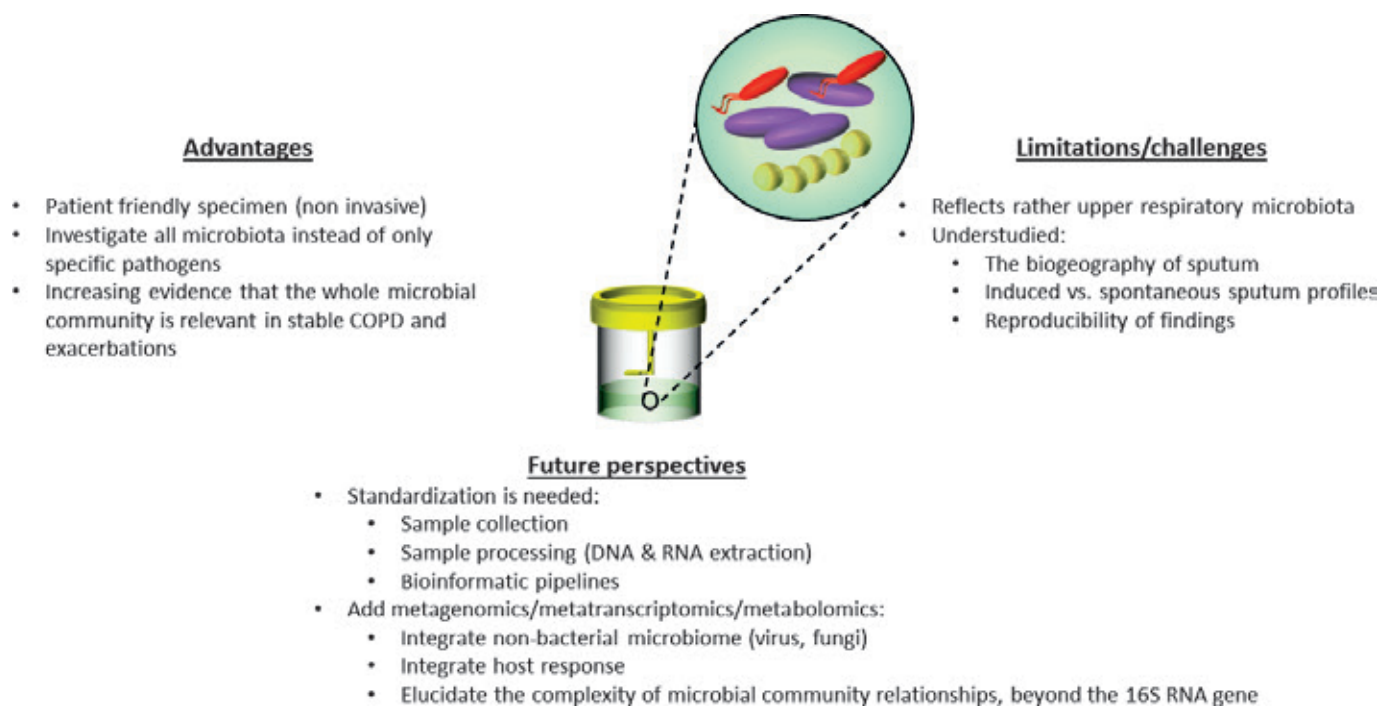


Figure 1 Sputum microbiome profiling - beyond singular pathogen detection. COPD, chronic obstructive pulmonary disease.

during exacerbations, preliminary results suggest that microbial composition may be affected by sampling technique.^{74–76} Furthermore, Gershman *et al* found that the duration of sputum induction affects the host cellular and biochemical composition in samples and suggest that the large airways are sampled at the beginning, whereas peripheral airways are sampled at later time periods.⁷⁷ Tangedal *et al* found that microbiota compositions differed between pairwise spontaneous and induced sputum samples in participants with COPD.⁷⁶ Further studies are needed in which protocols, and in particular sputum volume obtained, sample quality and procedure duration, are standardised across expectorated and induced sputum sampling.

Limitations and challenges: reproducibility of findings

COPD sputum microbiome studies to date have mainly used a cross-sectional design. Within-individual longitudinal microbial profiling reports are lagging, but data are starting to emerge. Sinha *et al* collected repeated induced sputum samples from four stable patients with COPD over 9 months. They reported the stability of bacterial composition and diversity over 2 days, with increased variability over 9 months.⁷⁸ In a larger longitudinal cohort (n=101), Mayhew *et al* found relative stability in microbial composition in a participant subset,⁵¹ while those with more variability were more likely to have higher exacerbation frequency.

Overall, both within-individual and between-cohort reproducibility represent crucial milestones in the development of a biomarker and require further scientific attention and evaluation with respect to sputum microbiome profiles in COPD.^{79,80}

Future perspectives: integrate the non-bacterial microbiome

16S rRNA sequencing approaches in sputum samples have provided important insights into the dynamics of the bacterial microbiome in stable COPD and exacerbations. However, the respiratory microbiome includes viruses and fungi as well as bacteria. The prevalence and clinical significance of fungi (mycobiome) in the respiratory tract in the context of COPD are particularly understudied.^{81–82} Bacterial-fungal and bac-

terial-viral interactions can affect microbial dynamics and microbe–host interactions and require further attention.^{83–84} Furthermore, the outgrowth of potentially pathogenic bacteria can be influenced by prior nonbacterial infections. Postviral bacterial respiratory infections are common overall. However, Molyneaux *et al* suggest that postviral bacterial dysbiosis is particularly an issue in COPD. They found that rhinovirus infection was followed by an outgrowth of *H. influenzae* in COPD sputum samples and associated with an increased neutrophilic inflammatory response.⁸⁵ They did not observe this outgrowth in healthy controls.

Overall, mechanisms of postviral secondary bacterial infections are known to be complex, mediated by interactions between viruses and bacteria (intermicrobial interactions) as well as the host immune system.⁸⁶ It will be crucial to evaluate not only bacterial microbiome dynamics but viral and fungal dynamics as well, to evaluate the influence of inter-microbial interactions on both homeostasis and pathogenesis within the respiratory tract. Shotgun metatranscriptomic approaches may be particularly well suited to these types of analyses as they can survey both bacterial and non-bacterial microbes and may provide an assessment of functional activity

Future perspectives: integrate the host response

Although technically challenging, high-throughput sequencing techniques, such as metatranscriptomics, offer the possibility to simultaneously sequence the host and microbial genomes.³⁶ In principle, host genome and microbiome profiles could be analysed in ‘one run’ in airway samples from COPD patients, offering the possibility to directly analyse the interactions between microbiota and the host immune profiles on a personal genome level. Langelier *et al* recently demonstrated how the integration of host response and microbiome profiling can contribute to diagnosis and characterisation of LRT infections (LRTI) in critically ill patients with acute respiratory failure, based on metagenomic and metatranscriptomic sequencing in tracheal aspirate samples.⁸⁷ Combining pathogen, microbiome and host gene expression metrics enhanced LRTI diagnosis in cases of unknown aetiology, showcasing the potential of this model to optimise diagnostics for airway diseases.

CONCLUSION

In conclusion, high-throughput sequencing techniques allow for an increasingly detailed assessment of the COPD airway microbiome. Sputum likely only partially represents the respiratory microbiome in COPD, given the enrichment for oral flora. However, the increasing evidence of sputum microbiome associations with characteristics of stable COPD and exacerbations, treatment response, and outcomes suggest that sputum microbiome profiling may provide important biomarkers to better understand COPD biology and guide therapies. Many outstanding questions remain. Answering these questions will take exacting studies implementing standardised protocols and employing the evolving technologies and statistical approaches to study microbial community structure in relation to the COPD relevant host response.

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A AOS infantil é um determinante independente de pressão arterial na idade adulta: estudo de seguimento longitudinal

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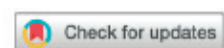
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RESUMO

Contexto A literatura atual apoia a associação transversal entre a apneia obstrutiva do sono (AOS) infantil e a pressão arterial (PA) elevada. No entanto, permanecem por explorar resultados cardiovasculares a longo prazo em crianças com AOS.

Objetivo Avaliar as associações da AOS infantil com parâmetros de PA em estudo prospetivo de seguimento de 10 anos.

Métodos Os participantes foram recrutados a partir de uma coorte estabelecida para o nosso estudo epidemiológico anterior sobre a AOS. Estes foram convidados a submeter-se a exame clínico, polissonografia noturna e monitorização ambulatória de PA de 24 horas por dia. Foi utilizada uma regressão linear multivariada para avaliar as associações da AOS infantil basal com os resultados de PA no seguimento. Foi utilizada a regressão log-binomial multivariada com ponderação de probabilidade inversa para avaliar as associações ajustadas de AOS infantil com hipertensão e não diminuição da PA noturna na idade adulta.

Resultados 243 participantes (59% do sexo masculino) compareceram à visita de seguimento. A idade média foi de 9,8 (DP $\pm 1,8$) e 20,2 (DP $\pm 1,9$) anos no início do estudo e no seguimento, respetivamente, com uma duração média de seguimento de 10,4 (DP $\pm 1,1$) anos. A AOS infantil moderada a grave foi associada a uma pressão arterial sistólica (PAS) noturna mais elevada (diferença em relação aos controlos normais: 6,5 mmHg, 95% IC 2,9 a 10,1) e uma redução da diminuição da pressão arterial sistólica noturna (-4,1%, 95% IC -6,3% a 1,8%) no seguimento, ajustado para idade, sexo, índice de massa corporal e altura no início do estudo, independentemente da presença de AOS no seguimento. A AOS infantil moderada a grave também foi associada a um maior risco de hipertensão (risco relativo (RR) 2,5, 95% IC 1,2 a 5,3) e não diminuição de PAS noturna (RR 1,3, 95% IC 1,0 a 1,7) no seguimento.

Conclusão Constatou-se que a AOS infantil é um fator de risco independente para resultados adversos de PA na idade adulta.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder that affects all ages. The reported prevalence is 3%–5% in children and 9%–38% in adults.^{1,2} It is an important disease because of its association with cardiovascular, metabolic and neurobehavioural complications.^{3–7} Studies have consistently demonstrated elevated blood pressure (BP), a well-known risk factor for cardiovascular and cerebrovascular adverse outcomes, in children^{4,6,8,9} and adults¹⁰ with OSA. Non-dipping of nocturnal BP (reduction of nocturnal BP <10% from daytime level) has also been demonstrated in both adults and children with OSA.^{11–18} The phenomenon of nondipping in nocturnal BP precedes the development of hypertension in normoten-

Mensagens-chave

What is the key question?

► Does childhood obstructive sleep apnoea (OSA) have any long-term effects on blood pressure (BP) in adulthood?

What is the bottom line?

► Childhood OSA is an independent determinant of adult BP.

Why read on?

► This is the first longitudinal 10-year follow-up study to evaluate the effects of childhood OSA on long-term cardiovascular outcomes in adulthood.

sive individuals. For patients with hypertension, non-dipping is associated with increased target organ damage and worse cardiovascular prognosis.¹¹ Therefore, prevention of BP abnormalities and non-dipping is important to reduce the risk of developing cardiovascular adverse events.¹⁹ If OSA was proven to be one of the contributing factors, its treatment or prevention may help to reduce future cardiovascular morbidities and mortality.

Longitudinal studies in adults have shown an independent dose-response relationship between OSA and hypertension.^{20–22} This positive association, however, is not demonstrated across all studies.^{23,24} Our previous study, one of a few paediatric longitudinal studies, found a significant association between childhood OSA and elevated BP at 4-year follow-up.⁴ The Penn State Child cohort reported an association between elevated systolic blood pressure (SBP) and vascular reactivity with new onset sleep-disordered breathing (SDB).^{25,26}

Vlahandonis *et al* showed that improvement of SDB over a 4-year period is accompanied by a significant improvement in nocturnal BP.²⁷ On the other hand, a 5-year follow-up study did not find any relationship between the presence of SDB and BP.²⁸ There are limitations in these published studies, namely, a relatively short follow-up period; only casual BP is measured in the majority of them; and the low SDB prevalence limits their study power. Whether childhood OSA is an independent determinant of adult BP outcomes remains undefined. Studies investigating the association between childhood OSA and nocturnal BP non-dipping have also yielded conflicting results. Some reported reduced nocturnal dipping in children with OSA or a reduction in dipping only in those with the most severe OSA,^{14–17} while others failed to find

any relationship at all.^{8 29 30} To our knowledge, no longitudinal studies have examined whether childhood OSA affects the dipping pattern of nocturnal BP in adulthood.

In this prospective 10-year follow-up study, we explored the associations between childhood OSA and ambulatory blood pressure (ABP) outcomes in early adulthood. We hypothesised that childhood OSA was associated with higher BP and reduced nocturnal BP dipping at follow-up.

METHODS

Participants

This was a prospective longitudinal follow-up study of a cohort established between 2003 and 2005 for a childhood OSA epidemiological study.^{1 31} Children aged 6–13 years were randomly recruited from local primary schools. Details of recruitment can be found in our previous publications.^{1 31} At baseline, a total of 619 participants underwent overnight polysomnography (PSG), 250 were healthy controls, 03 had primary snoring (PS) while 266 had OSA (refer to the PSG and definitions section for definitions). For this follow-up study, all subjects from the original cohort were invited to undergo PSG and ABP monitoring. They were excluded from participation if they had cardiovascular, renal and neuromuscular diseases, chromosomal abnormalities or acute illness within 2 weeks of PSG. Written informed consent and assent were obtained from the parents and participants, respectively.

Data collection and anthropometric measurements

Parents completed a validated personal data and sleep symptom questionnaire at baseline, and the participants did so at follow-up.³² The weight and height of the subjects were measured on the day they underwent the PSG. Standing height without shoes was documented using a Harpenden stadiometer (Holtain, UK) to the nearest 0.1cm. Body weight (with the lightest clothing) measured to the nearest 0.1kg was obtained by an electronic weighing scale (Tanita BF-522, Japan). Body Mass Index (BMI) was calculated as weight/height² (kg/m²) and converted to z-scores appropriate for age and sex according to local reference.³³ Overweight and obesity were defined as BMI z-scores of ≥ 1.036 and 1.645, corresponding to

the 85th and 95th percentiles, respectively. Pubertal stage at baseline visit was evaluated using a validated self-assessment questionnaire.³⁴

PSG and definitions

Nocturnal PSG was carried out at the Prince of Wales Hospital. Baseline PSG was performed, manually edited and scored as described.^{1 34 6} At follow-up, Siesta ProFusion III PSG monitor (Compumedics Telemed, Abbotsford, Victoria, Australia) was used to record the following parameters: electroencephalogram (F4/A1, C4/A1 and O2/A1), bilateral electro-oculogram, electromyogram of mentalis activity and bilateral anterior tibialis. Respiratory movements of the chest and abdomen were measured by inductance plethysmography. ECG and heart rate were continuously recorded from two anterior chest leads. Arterial oxyhaemoglobin saturation (SaO₂) was measured by a finger probe oximeter. Respiratory airflow pressure signal was obtained via a nasal catheter placed at the anterior nares and connected to a pressure transducer. An oronasal thermal sensor was used to detect absent airflow. Snoring was measured by a microphone placed near the throat. Body position was monitored via a body position sensor.

Respiratory events including obstructive apnoeas, mixed apnoeas, central apnoeas and hypopnoeas were scored based on the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events V.2.0.35 Respiratory effort-related arousals (RERAs) were scored when there was an arousal with a fall of $<50\%$ from baseline in the amplitude of nasal pressure signal with flattening of the nasal pressure waveform, accompanied by snoring, noisy breathing or evidence of increased effort of breathing. A respiratory event was scored when it lasted ≥ 2 breaths irrespective of its duration for children at baseline, and 10s for adolescents and adults at follow-up based on the AASM recommendations.³⁵ Arousal was defined as an abrupt shift in electroencephalogram frequency during sleep, which may include theta, alpha and/or frequencies greater than 16Hz but not spindles, with 3–15s in duration. In rapid eye movement sleep, arousals were scored only when accompanied by concurrent increase in submental electromyography amplitude.³⁵

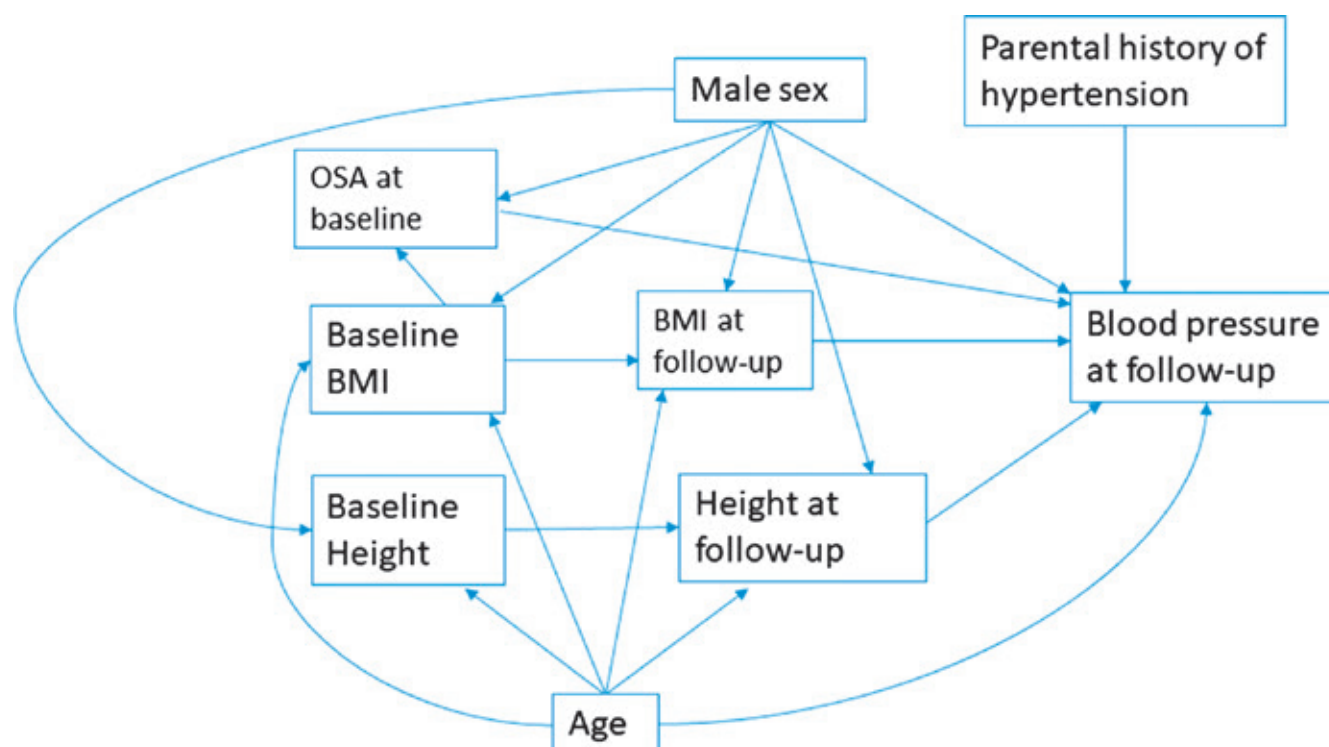


Figure 1 Potential relationships between exposures and blood pressure outcomes at follow-up. BMI, body mass index; OSA, obstructive sleep apnoea.

Table 1 Characteristics of subjects with different baseline OSA severity

	Normal	Primary snoring	Mild OSA	Moderate-to-severe OSA	
Subject characteristics	n=98	n=49	n=75	n=21	P for trend*
Male sex, n (%)	51 (52.0)	29 (59.2)	51 (68.0)	16 (76.2)	0.009
Prepubertal at baseline, n (%)	83 (84.7)	47 (95.9)	65 (86.7)	19 (90.5)	0.53
Age (years)					
Baseline	9.9±1.8	9.3±1.8	9.9±1.8	9.7±1.9	0.94
Follow-up	20.3±2.0	20.0±1.9	20.3±1.9	19.5±2.1	0.34
Follow-up length (years)	10.4±1.0	10.7±0.9	10.3±1.1	9.8±1.1	0.10
Height (cm)					
Baseline	135.3±11.9	132.2±11.6	136.8±11.6	135.8±13.0	0.46
Follow-up	166.5±8.4	166.8±8.8	168.8±9.4	168.4±7.7	0.088
BMI (kg/m ²)					
Baseline	17.4±3.1	17.5±2.9	18.5±3.2	19.0±3.7	0.008
Follow-up	21.9±4.4	21.8±3.2	22.3±3.7	22.0±4.4	0.55
BMI z-score					
Baseline	0.30±1.03	0.49±0.85	0.65±1.00	0.80±1.12	0.007
Follow-up	0.18±1.18	0.29±0.85	0.40±1.04	0.31±1.01	0.25
Overweight, n (%)					
Baseline	26 (26.5)	14 (28.6)	27 (36.0)	10 (47.6)	0.044
Follow-up	21 (21.4)	9 (18.4)	16 (21.3)	5 (23.8)	0.88
Habitual snoring, n (%)					
Baseline	0 (0.0)	49 (100.0)†	23 (30.7)†	9 (42.9)†	<0.001
Follow-up	12 (12.2)	17 (34.7)†	20 (26.7)†	4 (19.0)	0.073
OAHl (events/hour)					
Baseline	0.1 (0–0.4)	0.2 (0–0.5)	1.9 (1.2–2.8)†	7.5 (5.8–10.3)†	<0.001
Follow-up	0.7 (0–3.7)	1.5 (0.5–5.5)	1.7 (0.4–4.7)†	5.3 (1.4–8.7)†	0.002
ODI (events/hour)					
Baseline	0.1 (0–0.3)	0.2 (0–0.5)	0.5 (0.2–1.1)†	3.2 (1.4–5.2)†	<0.001
Follow-up	1.3 (0.3–4.0)	0.9 (0.2–3.7)	2.1 (0.7–5.8)	3.7 (1.3–7.0)†	0.013
Arousal Index (events/hour)					
Baseline	5.7 (4.6–7.7)	6.1 (4.7–7.7)	7.1 (5.3–8.5)†	10.3 (8.0–13.1)†	<0.001
Follow-up	11.6 (9.0–15.6)	12.5 (9.3–16.5)	11.6 (9.5–15.1)	16.5 (12.8–21.9)†	0.007
Parental history of hypertension, n (%)					
Father	21 (21.4)	15 (30.6)	21 (28.0)	7 (33.3)	0.20
Mother	19 (19.4)	9 (18.4)	13 (17.3)	3 (14.3)	0.58
Either parent	34 (34.7)	19 (38.8)	30 (40.0)	9 (42.9)	0.38
Both parents	6 (6.1%)	5 (10.2)	4 (5.3)	1 (4.8)	0.75

*P values obtained from linear contrast tests and linear-by-linear association tests for continuous and categorical data, respectively.

†p<0.05 after Bonferroni adjustment, compared with the normal group.

BMI, Body Mass Index; OAHl, Obstructive Apnoea–Hypopnoea Index; ODI, Oxygen Desaturation Index; OSA, Obstructive Sleep Apnoea.

Obstructive Apnoea–Hypopnoea Index (OAHl) was defined as the total number of obstructive and mixed apnoeas and hypopnoeas per hour of sleep. Respiratory Disturbance Index was defined as the total number of obstructive and mixed apnoeas, hypopnoeas and RERAs per hour of sleep. Oxygen Desaturation Index (ODI) was defined as the total number of dips in arterial oxygen saturation $\geq 3\%$ per hour of sleep. Arousal Index was the total number of arousals per hour of sleep. Respiratory Arousal Index was the total number of arousals per hour of sleep that were associated with apnoea, hypopnoea or flow limitation.

OSA at baseline was defined by an OAHl of ≥ 1 event/hour. Mild childhood OSA was defined as an OAHl between 1 and 5 events/hour, while moderate-to-severe childhood OSA was defined as an OAHl of ≥ 5 events/hour. OSA at follow-up was defined by an OAHl of ≥ 5 events/hour as the subjects had already reached late adolescence or early adulthood.³⁶ Mild adult OSA was defined by an OAHl between 5 and 15 events/hour, while moderate-to-severe OSA was defined by an OAHl of ≥ 15 events/hour. Primary snoring was defined when a subject had self-reported or parent-reported habitual snoring (at least three nights per week) in the past 12 months with an OAHl below the diagnostic cut-off for OSA. Same definitions were adopted in our recent publication on the natural history of childhood OSA.³¹

ABP measurement

All participants underwent 24-hour ABP monitoring, which was carried out on the day of overnight PSG with a validated oscillometric monitor (Spacelabs 90217, Spacelabs Healthcare). The proper-sized cuff was placed on the non-dominant arm. SBP, diastolic blood pressure (DBP) and mean arterial pressure (MAP) were measured every 30min during the period from 21:30 to 07:30 (nocturnal sleep period) and every 15min outside of this period (daytime wake period). The exact cut-off dividing wake and sleep BP were defined according to the PSG tracings. Individual mean SBP and DBP were calculated for wake and sleep periods. Recordings were accepted if there were at least 40 successful readings for the entire 24-hour period with a minimum of one successful reading per hour.³⁷ Hypertension at baseline was defined when SBP or DBP at daytime, night-time or over a 24-hour period was ≥ 95 th percentile with reference to height based on local norms.³⁸ Hypertension at follow-up was defined as having SBP at daytime, night-time and 24 hours of ≥ 135 , 120 and 130mm Hg, respectively; or DBP at daytime, nighttime and 24 hours of ≥ 85 , 70 and 80mm Hg, respectively.³⁹ Degree of nocturnal dipping was calculated as the percentage drop of BP from wakefulness to sleep [(wake BP–sleep BP)/wake BP $\times 100\%$].^{4–11} Non-dipping of nocturnal BP was defined as $<10\%$ nocturnal drop of BP.¹¹

Table 2 Baseline and follow-up BP of subjects by baseline OSA severity

BP parameters	Normal n=98	Primary snoring n=49	Mild OSA n=75	Moderate-to-severe OSA n=21	P for trend*
Daytime SBP (mm Hg)					
Baseline†	112±10	112±7	113±8	114±7	0,35
≥95th percentile, n (%)	0 (0)	0 (0)	1 (1.7)	0 (0)	0,38
Follow-up‡	115±9	116±10	117±10	118±8	0,076
≥135 mm Hg, n (%)	1 (1.0)	3 (6.1)	3 (4.0)	0 (0.0)	0,59
Daytime DBP (mm Hg)					
Baseline†	71±6	73±6	72±6	73±4	0,20
≥95th percentile, n (%)	1 (1.3%)	2 (6.1)	2 (3.4%)	0 (0.0)	0,81
Follow-up‡	72±6	73±6	73±6	72±5	0,68
≥85 mm Hg, n (%)	2 (2.0)	3 (6.1)	4 (5.3)	0 (0.0)	0,67
Night-time SBP (mm Hg)					
Baseline†	99±10	98±6	101±8	106±11§	0,011
≥95th percentile, n (%)	10 (13.2)	0 (0.0)	6 (10.3)	5 (29.4)	0,36
Follow-up‡	103±9	104±9	104±9	111±10§	0,007
≥120 mm Hg, n (%)	3 (3.1)	1 (2.0)	4 (5.4)	6 (28.6)§	0,001
Night-time DBP (mm Hg)					
Baseline†	59±6	58±5	59±5	62±6	0,19
≥95th percentile, n (%)	12 (15.8)	2 (6.1)	8 (13.8)	5 (29.4)	0,47
Follow-up‡	62±6	63±7	62±6	64±7	0,45
≥70 mm Hg, n (%)	9 (9.3)	8 (16.3)	9 (12.2)	2 (9.5)	0,73
Any hypertension, n (%)					
Baseline†	17 (22.4)	3 (9.1)	12 (20.7)	7 (41.2)	0,33
Follow-up‡	11 (11.3)	11 (22.4)	14 (18.9)	6 (28.6)	0,053
SBP nocturnal dipping (%)					
Baseline†	11.4±5.0	12.8±4.9	9.9±5.7	7.6±7.4§	0,009
Follow-up‡	10.1±4.8	9.6±6.0	10.5±5.4	6.3±5.7§	0,15
SBP non-dipping, n (%)					
Baseline†	29 (38.2)	9 (27.3)	25 (43.1)	11 (64.7)	0,097
Follow-up‡	53 (54.6)	27 (55.1)	35 (47.3)	17 (81.0)	0,48
DBP nocturnal dipping (%)					
Baseline†	17.3±6.7	19.7±7.4	17.8±5.8	15.8±7.2	0,78
Follow-up‡	14.5±6.4	14.2±7.5	15.2±6.3	11.9±8.0	0,60
DBP non-dipping, n (%)					
Baseline†	10 (13.2)	2 (6.1%)	6 (10.3)	3 (17.6)	0,97
Follow-up‡	22 (22.7)	16 (32.7)	14 (18.9)	7 (33.3)	0,84

*P values obtained from linear contrast tests and linear-by-linear association tests for continuous and categorical data, respectively.

†59 missing.

‡2 missing.

§P <0.05 after Bonferroni adjustment, compared with the normal group.

BP, Blood Pressure; DBP, Diastolic Blood Pressure; OSA, Obstructive Sleep Apnoea; SBP, Systolic Blood Pressure.

Sample size

Assuming a follow-up rate of 40% of total 619 children with 40%, 20%, 31% and 9%, respectively, were normal controls, primary snorers, having mild and moderate-to-severe OSA at baseline, a sample size of 20–80 in each group with different OSA severity at baseline and 100 normal controls would be sufficient to detect an effect size of 0.4 (equivalent to 3.9mm Hg SBP and 2.5mm Hg DBP) to 0.7 (equivalent to 6.8mm Hg SBP and 4.3mm Hg DBP) between OSA and control groups, with a statistical power of 80% and an alpha of 5%

Statistical analysis

χ^2 tests, t-tests and Mann-Whitney U tests with Bonferroni corrected p values were used to assess differences in baseline characteristics by inclusion in the 10-year follow-up for categorical, normally distributed and non-normally distributed data, respectively. Linear contrast tests and linear-by-linear association tests with Bonferroni corrected p values for continuous and categorical data, respectively, to assess differences in baseline characteristics and BP at baseline and follow-up by baseline OSA severity and by childhood OSA status. We used Pearson correlation to assess the correlations of SBP and DBP (daytime, night-time and dipping) at follow-up with height, BMI and logtransformed OAH1 at follow-up. Multivariate

linear regression was used to assess the associations of baseline childhood OSA status with SBP, DBP and dipping of nocturnal BP at follow-up.

Potential confounders, defined as factors potentially related to childhood OSA and BP outcomes in adulthood, were sex, age, BMI, height and parents' self-reported hypertension (either parent vs none) at baseline (figure 1). Robustness of the results was examined by additionally adjusting for other potential confounders for BP outcomes, including OAH1 and ODI at follow-up in subsequent models. We tested whether the associations of childhood OSA (log-transformed OAH1) and BP in adulthood differed by sex, age/pubertal staging at baseline, BMI, OAH1 and oxygen saturation at follow-up. To assess the adjusted associations of childhood OSA with risks of hypertension and non-dipping of nocturnal BP in adulthood, multivariable logbinomial regression was used with inverse probability weighting and relative risks (RRs) with 95% CIs reported. To generate the inverse probability weights of response for each included participant in the regression analysis, logistic regression on baseline predictors was built to estimate the probability of being included in the follow-up. Statistical analyses were performed using R V.3.3.2 (R Development Core Team, Vienna, Austria) and SPSS statistical software package V.21.0 for Windows.

RESULTS

Sample characteristics

From the original 619 participants, 243 (59% male) attended the 10-year follow-up visit, giving a response rate of 39%. Detailed characteristics of the participants have been reported in our recent publication.³¹ The mean age of the respondents at follow-up was 20.2 ± 1.9 years, ranging from 16.1 to 25.0 years. Higher proportion of participants with childhood primary snoring and lower proportion of those with moderate-to-severe childhood OSA attended. However, baseline characteristics of the respondents were comparable to the non-respondents except that former with mild childhood OSA had a higher prevalence of allergic rhinitis ($p=0.049$)³¹ (online supplementary table 1).

Forty per cent, 20%, 31% and 9% of the participants, respectively, were normal controls and primary snorers having mild and moderate-to-severe OSAs at baseline. At baseline, OSA was associated with higher BMI z-score and a higher prevalence of parent-reported habitual snoring (table 1). Participants with moderate-to-severe childhood OSA had higher nocturnal SBP at both baseline and follow-up, and they were more likely to have nocturnal systolic hypertension and reduced nocturnal dipping of SBP at follow-up (table 2).

At follow-up ABP was available in all but two participants with insufficient successful measurements and their results were excluded. One participant with outlying OAH1 (80.9 events/hour) at baseline was also excluded. Characteristics at baseline and follow-up by OSA categories at follow-up are shown in online supplementary table 2. Respectively 64%, 12%, 16% and 8% were classified as normal, having primary snoring, mild OSA and moderate-to-severe OSA at follow-up. Majority of those who had moderate-to-severe OSA were male, they also had higher BMI z-score, higher daytime SBP and DBP, and higher nocturnal SBP at follow-up (online supplementary table 2). The positive correlations of ABP with height, BMI and log OAH1 at follow-up were more significant for SBP compared with DBP (figure 2). Nocturnal BP dipping in both SBP and DBP did not correlate with height, BMI and OAH1 at follow-up (figure 2).

Associations of baseline OSA with BP outcomes at follow-up

Compared with participants who were disease free, those with moderate-to-severe OSA at baseline, but not mild OSA or primary snoring, had higher nocturnal SBP and reduced nocturnal SBP and MAP dipping at follow-up, after adjusting for sex, age, BMI, height and parental hypertension (table 3). Adjusted nocturnal SBP at follow-up was 6.5 mm Hg (95%CI 2.9 to 10.1) higher, and the adjusted degree of nocturnal SBP dipping was 4.1% (95% CI -6.3% to 1.8%) lower in those with childhood moderate-to-severe OSA than those without OSA ($p<0.05$). The significant differences remained after additional adjustment for BMI, OAH1 and ODI at follow-up. These associations did not vary by sex, age at baseline, BMI or OAH1/ODI at follow-up.

Moderate-to-severe OSA at baseline compared with participants who were disease-free was associated with higher risk of hypertension (RR 2.5, 95%CI 1.2 to 5.3) and non-dipping in nocturnal SBP (RR 1.3, 95%CI 1.0 to 1.7) and MAP (RR 1.8, 95%CI 1.3 to 2.4) after adjusting for sex, age, BMI and height at baseline, height at follow-up and parental hypertension. This association however, was not demonstrated in nocturnal diastolic hypertension or non-dipping of DBP (table 4). Moreover, moderate-to-severe OSA at baseline was significantly associated with higher nocturnal SBP and reduced SBP dipping regardless of OSA status at follow-up after adjusting for sex, age, BMI and height at baseline, height at follow-up and parental hypertension (table 5). There was a trend that individuals with both childhood moderate-to-severe OSA and adult OSA had higher SBP at follow-up than those who had only childhood disease (table 5).

DISCUSSION

This prospective 10-year follow-up study showed that moderate-to-severe childhood OSA was independently and significantly associated with higher nocturnal SBP, hypertension and reduced nocturnal dipping of SBP in early adulthood. Our findings supported childhood OSA as an independent determinant of BP outcomes in adulthood and could be a potentially modifiable childhood factor contributing to future development of hypertension and other cardiovascular adverse outcomes. A threshold effect was also evident as only more severe OSA was associated with longer-term adverse BP outcomes.

While multiple cross-sectional studies have demonstrated the association between OSA and elevated BP, data from longitudinal follow-up studies are valuable in terms of evidence hierarchy in supporting this association. Our findings are consistent with our previous work that documented OSA severity to be independently associated with BP measurements at 4-year follow-up in non-obese children.⁴ The current study further identified that this association remained so regardless of the participants' OSA severity at follow-up. Although there was a trend where individuals with both childhood and adult OSAs had higher SBP at follow-up than those who had only childhood OSA, the associations between moderate-to-severe childhood OSA and worse adult BP outcomes were independent of their current OSA status. This may suggest OSA-related vascular remodelling can begin early in childhood and leads to persistent BP abnormalities. This underscores the importance of early recognition and treatment of childhood OSA. Nonetheless, studies that examined BP at follow-up as a primary outcome in children with SDB have reported conflicting results.^{27 40–42}

Decline in overnight beat-to-beat BP in children with improved SDB is found in a 4-year follow-up study.²⁷ A significant reduction in DBP readings using office BP in children with resolved OSA was documented at follow-ups of 1 year and 2–14 months.^{40 41} However, no difference in BP measurements at baseline and follow-up is demonstrated using ABP monitoring.⁴² Different sampling frame, BP monitoring tools and mix of patients with varying degrees of OSA severity could explain the aforementioned reported findings. A randomised controlled study to evaluate the effects of OSA intervention on BP parameters with repeated follow-up assessments is required to ascertain the possible causative role of childhood OSA on long-term BP.

Only moderate-to-severe childhood OSA was associated with worse BP outcomes, suggesting a threshold effect of OSA on BP control. This finding is consistent with previous reports on the cross-sectional association between OSA severity, cardiac function and structure and BP levels. Significantly higher BP, presence of nocturnal hypertension and ventricular dysfunction are seen only in more severe childhood OSA.^{3 6 43} In contrast, neurocognitive deficits, another important sequelae in children with OSA, are present even in those with primary snoring.⁴⁴ Detailed delineation of the different PSG parameters, together with better OSA phenotyping, will explain the differential effects of OSA on clinical outcomes. Nocturnal rather than daytime BP measurements were associated with OSA in this study. This is explainable as mediating events, namely, abnormal gaseous exchange, arousals and sympathetic activation, take place during sleep.¹¹ Other yet to be determined processes are likely to be involved as cross-sectional studies have shown higher nocturnal BP in childhood OSA even after exclusion of respiratory events. Elevated daytime BP is also documented in children with OSA.^{8 9 45} The mechanism to explain this phenomenon is not completely understood and requires further examination. The differential effect on SBP but not DBP has previously been reported.^{43 46} The exact reason underlying this occurrence has not been fully elucidated.

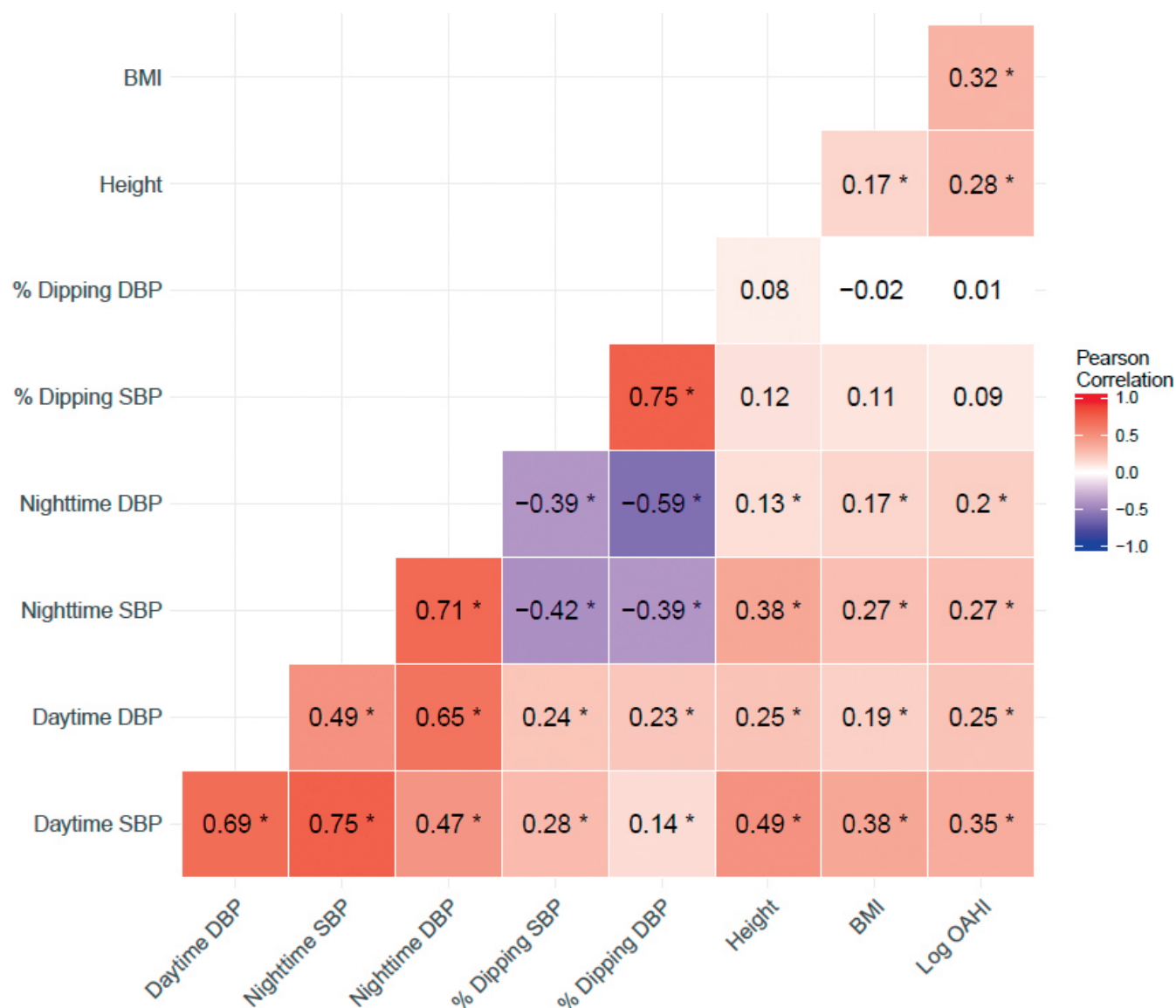


Figure 2 Heat map showing correlations of SBP and DBP (daytime, night-time and dipping) at follow-up with height, BMI and log-transformed OAHl at follow-up. * $P < 0.05$. BMI, body mass index; DBP, diastolic blood pressure; OAHl, obstructive apnoea–hypopnea index; SBP, systolic blood pressure.

ted; it is proposed that SBP is more vulnerable to intermittent hypoxia and sympathetic activation.^{43–46} Whether prolonged disease would lead to ‘overspill’ and cause daytime and DBP abnormalities should be examined. Nocturnal BP dipping is a physiological phenomenon, the absence of which precedes the development of cardiovascular adverse events.¹¹

Our previous 4-year follow-up study did not show significant differences in nocturnal BP dipping among groups with varying baseline OSA severity.⁴ In contrast, this current study demonstrated an association between moderate-to-severe childhood OSA with reduced nocturnal SBP dipping in adulthood. This may suggest the effects of OSA on BP dipping profile do take time to develop. The mechanism by which childhood OSA affects BP was not examined in our current study. We demonstrated that the adverse effects on BP were independent of the subjects’ OSA status at follow-up. A likely mechanism was the tracking of higher BP from childhood to adulthood, particularly in those who had moderate-to-severe OSA at baseline.⁴⁷ BP abnormalities and reduced nocturnal BP dipping are well known risk factors for stroke, cardiovascular disease and end-stage renal disease.^{11–19} Childhood OSA as shown in this study is a potentially modifiable parameter leading to these adverse outcomes.

Tackling childhood OSA could theoretically reduce future cardiovascular disease burden in our society and can have far-reaching public health implications. Paediatricians should rou-

tinely ask about OSA symptoms in their practice, and patients suspected to have the condition should be promptly evaluated and managed accordingly. Our study was the first prospective longitudinal study to examine a cohort of participants from childhood to adulthood to evaluate the effects of OSA on cardiovascular outcomes. There were a few limitations to address. Participation rate of subjects from our original cohort was low and there was a possibility of selection bias. Inverse probability weighting was used to minimise such potential biases. Baseline characteristics including age, sociodemographic parameters, pubertal status, weight and self-reported sleep problems were comparable between respondents and non-respondents. Although our study showed that moderate-to-severe childhood OSA was associated with worse BP outcomes in early adulthood regardless of their current OSA status, participants received different treatments at variable time points. In our cohort, 20% of children with OSA underwent surgery, while 14% received medical therapy such as intranasal corticosteroids.

Many declined treatment primarily because they were recruited from the community and in their parents’ perspective were relatively asymptomatic. There was heterogeneity to the timing of OSA resolution, and whether resolution was secondary to treatment or part of its natural history is unknown. As a result, the effects of OSA treatment on BP outcomes could not be assessed.

Table 3 Differences in ambulatory BP indices at 10-year follow-up (95% CI) by OSA status at baseline using normal as reference

BP parameters	Model	OSA status at baseline				P for interaction ‡				
		Normal n=98 (40%)	Primary snoring n=49 (20%)	Mild OSA n=75 (31%)	Moderate/severe OSA n=21 (8.6%)	Sex	Age (baseline)	BMI (follow-up)	OAI (follow-up)	ODI (follow-up)
SBP (mm Hg) (daytime)	1	Ref	0.0 (−3.0 to 3.6)	0.0 (−2.5 to 2.5)	1.6 (−1.9 to 5.2)	0,91	0,02*	0,74	0,49	0,09
	2	Ref	0.5 (−2.4 to 3.3)	0.4 (−1.9 to 2.8)	2.6 (−0.7 to 6.0)					
	3	Ref	−0.1 (−3.1 to 2.8)	−0.1 (−2.5 to 2.4)	1.0 (−2.5 to 4.5)					
	4	Ref	−0.2 (−3.3 to 2.9)	0.0 (−2.5 to 2.6)	1.6 (−2.3 to 5.6)					
SBP (mm Hg) (night-time)	1	Ref	1.0 (−2.1 to 4.2)	−0.4 (−3.0 to 2.2)	6.5*** (2.9 to 0.1)	0,58	0,11	0,44	0,54	0,58
	2	Ref	1.3 (−1.8 to 4.3)	−0.2 (−2.7 to 2.3)	7.1*** (3.5 to 10.7)					
	3	Ref	0.8 (−2.3 to 3.9)	−0.6 (−3.1 to 2.0)	6.0** (2.4 to 9.7)					
	4	Ref	0.6 (−2.6 to 3.9)	−0.5 (−3.2 to 2.2)	7.0*** (2.9,11.1)					
SBP (% dipping)	1	Ref	−0.9 (−2.9 to 1.0)	0.4 (−1.3 to 2.0)	−4.1*** (−6.3 to −1.8)	0,36	0,48	0,36	0,62	0,25
	2	Ref	−0.8 (−2.8 to 1.1)	0.4 (−1.2 to 2.1)	−3.8** (−6.1 to −1.5)					
	3	Ref	−1.0 (−2.9 to 1.0)	0.3 (−1.3 to 2.0)	−4.8*** (−6.5 to −1.9)					
	4	Ref	−0.8 (−3.0 to 1.3)	0.3 (−1.5 to 2.1)	−4.5** (−7.2 to −1.7)					
DBP (mm Hg) (daytime)	1	Ref	0.9 (−1.3 to 3.2)	0.3 (−1.5 to 2.2)	−0.2 (−2.8 to 2.4)	0,73	0,06	0,34	0,46	0,30
	2	Ref	1.1 (−1.1 to 3.3)	0.5 (−1.3 to 2.3)	0.2 (−2.4 to 2.8)					
	3	Ref	0.8 (−1.4 to 3.0)	0.3 (−1.5 to 2.1)	−0.6 (−3.1 to 2.0)					
	4	Ref	0.7 (−1.6 to 3.1)	0.5 (−1.5 to 2.4)	1.0 (−2.0 to 3.9)					
DBP (mm Hg) (night-time)	1	Ref	1.2 (−1.2 to 3.5)	−0.2 (−2.2 to 1.7)	1.8 (−1.0 to 4.5)	0,76	0,06	0,56	0,42	0,73
	2	Ref	1.3 (−1.0 to 3.7)	−0.1 (−2.0 to 1.9)	2.1 (−0.6 to 4.9)					
	3	Ref	1.0 (−1.3 to 3.3)	−0.3 (−2.3 to 1.6)	1.3 (−1.4 to 4.1)					
	4	Ref	1.0 (−1.5 to 3.4)	−0.5 (−2.5 to 1.6)	2.5 (−0.6 to 5.6)					
DBP (% dipping)	1	Ref	−0.5 (−3.1 to 2.0)	0.8 (−1.3 to 2.9)	−2.6† (−5.6 to 0.3)	0,42	0,90	0,54	0,73	0,57
	2	Ref	−0.6 (−3.1 to 1.9)	0.7 (−1.4 to 2.8)	−2.7† (−5.7 to 0.3)					
	3	Ref	−0.5 (−3.1 to 2.0)	0.8 (−1.3 to 2.9)	−2.6† (5.6 to 0.4)					
	4	Ref	−0.6 (−3.2 to 2.1)	1.2 (−1.1 to 3.4)	−2.2 (−5.6 to 1.12)					
MAP (mm Hg) (daytime)	1	Ref	0.5 (−1.6 to 2.6)	0.5 (−1.2 to 2.2)	0.7 (−1.8 to 3.1)	0,67	0,01*	0,28	0,75	0,11
	2	Ref	0.7 (−1.3 to 2.8)	0.7 (−0.9 to 2.4)	1.2 (−1.2 to 3.6)					
	3	Ref	0.4 (−1.7 to 2.4)	0.4 (−1.3 to 2.1)	0.2 (−2.2 to 2.7)					
	4	Ref	0.3 (−1.9 to 2.4)	0.6 (−1.2 to 2.4)	1.3 (−1.4 to 4.1)					
MAP (mm Hg) (night-time)	1	Ref	0.5 (−1.7 to 2.8)	−0.2 (−2.1 to 1.7)	3.0* (0.4 to 5.6)	0,64	0,15	0,79	0,64	0,76
	2	Ref	0.7 (−1.5 to 2.9)	−0.1 (−1.9 to 1.8)	to 3.4* (0.8 to 6.0)					
	3	Ref	0.4 (−1.9 to 2.6)	−0.3 (−2.2 to 1.5)	2.6† (−0.0,5.2)					
	4	Ref	0.4 (−2.0 to 2.7)	−0.4 (−2.3 to 1.6)	3.7* (0.7 to 6.6)					
MAP (% dipping)	1	Ref	−0.2 (−2.2 to .8)	0.8 (−0.8 to 2.5)	−2.7* (−5.0 to −0.3)	0,29	0,45	0,28	0,93	0,34
	2	Ref	−0.2 (−2.2 to 1.8)	0.9 (−0.8 to 2.5)	−2.6* (−5.0 to −0.3)					
	3	Ref	−0.2 (−2.3 to 1.8)	0.8 (−0.9 to 2.5)	−2.7* (−5.1 to −0.4)					
	4	Ref	−0.2 (−2.4 to 1.9)	1.0 (−0.8 to 2.8)	−2.8* (−5.5 to −0.1)					

Model 1 adjusted for sex, age, BMI at baseline and height at baseline, height at follow-up and parental self-reported hypertension (either parent vs none).

Model 2 adjusted for all variables in model 1 plus BMI at follow-up.

Model 3 adjusted for all variables in model 1 plus OAI at follow-up.

Model 4 adjusted for all variables in model 1 plus ODI at follow-up.

*P<0.05, **P<0.01, ***P<0.001.

†P<0.10.

‡Interaction term of log-transformed OAI with variable undertested.

BMI, Body Mass Index; BP, Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; OAI, Obstructive Apnoea–Hypopnoea Index; ODI, Oxygen Desaturation Index; OSA, Obstructive Sleep Apnoea; Ref, Reference; SBP, Systolic Blood Pressure.

It also highlighted the importance of following up subjects with moderate-to-severe childhood OSA even after intervention. We used 24-hour ABP monitoring, which provided a more accurate reflection of BP trend, pattern and diurnal variation.¹⁸ This monitoring tool might cause arousals during cuff inflation and potentially alter BP measurements.⁴⁸ However, it was shown in a previous study that sleep disturbance is minimal.¹⁷ Finally, data regarding factors that could influence BP control, such as dietary habit and exercise, were not recorded.

CONCLUSION

Our follow-up study demonstrated an independent association between childhood OSA with adverse BP outcomes in early adulthood. Future studies should investigate whether

OSA treatment would lessen one's risk of developing BP abnormalities, and if proven, targeting this modifiable childhood factor would be a way forward to reduce future cardiovascular disease burden.

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Table 4 Relative risks (95% CI) of any hypertension and BP non-dipping at 10 year follow-up by OSA status at baseline

		OSA status at baseline			
BP parameters	%	Normal	Primary snoring	Mild OSA	Moderate/severe OSA
Any hypertension	17	1.0	1.9† (0.9 to 4.2)	1.5 (0.7 to 3.0)	2.5* (1.2 to 5.3)
Non-dipping					
SBP	47	1.0	1.0 (0.8 to 1.4)	0.8 (0.6 to 1.1)	1.3* (1.0 to 1.7)
DBP	24	1.0	1.7† (1.0 to 2.9)	0.8 (0.4 to 1.5)	1.7† (1.0 to 2.9)
MAP	46	1.0	1.3 (0.9 to 1.9)	1.0 (0.7 to 1.5)	1.8*** (1.3 to 2.4)

Adjusted for sex, age, Body Mass Index and height at baseline, height at follow-up and parental self-reported hypertension (either parent vs none).

* $P<0.05$, ** $P<0.01$, *** $P<0.001$.

†P<0.10.

BP, Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; OSA, Obstructive Sleep Apnoea; SBP, Systolic Blood Pressure.

cript, and approved the final manuscript as submitted. all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Table 5 Differences in SBP indices at 10-year follow-up (95% CI) by OSA status at baseline using normal as reference in participants with/without OSA at follow-up

Outcome measures	OSA status at baseline				
	OSA status at follow-up	Normal	PS	Mild	Moderate/severe
Nocturnal SBP (mm Hg)	No OSA	Ref	1.8 (−1.8 to 5.3)	0.4 (−2.6 to 3.3)	6.2* (0.4 to 12.0)
	OSA	4.1† (−0.4 to 8.6)	2.0 (−3.5 to 7.5)	0.8 (−3.5 to 5.2)	8.1*** (3.6 to 12.5)
SBP nocturnal dipping (%)	No OSA	Ref	−2.2* (−4.5 to −0.0)	−0.5 (−2.4 to 1.3)	−5.5** (−9.1 to −2.0)
	OSA	−2.3† (−5.1 to 0.5)	1.2 (−2.2 to 4.6)	1.4 (−1.3 to 4.1)	−3.9** (−6.7 to −1.1)

Adjusted for sex, age, Body Mass Index and height at baseline, height at follow-up and parental self-reported hypertension (either parent vs none).

* $P<0.05$. ** $P<0.01$. *** $P<0.001$.

†P<0.10.

OSA, Obstructive Sleep Apnoea; OSA, obstructive sleep apnoea; OSA, Obstructive Sleep Apnoea; OSA, Obstructive Sleep Apnoea; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure.

Systolic Blood Pressure; OSA, Obstructive Sleep Apnoea; OSA, obstructive sleep apnoea; OSA, Obstructive Sleep Apnoea; OSA, Obstructive Sleep Apnoea; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure; SBP, Systolic Blood Pressure.

Gestão de suspeitas clínicas elevadas de doentes com COVID-19 internados com RTPCR negativo: um papel pragmático e limitado da TC torácica

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As the COVID-19 pandemic sweeps across the UK there remain issues with reverse transcription polymerase chain reaction (RT-PCR), the gold standard diagnostic method. Delays in obtaining results have been particularly problematic. Some patients, including those with high clinical suspicion of COVID-19, test falsely negative on initial RT-PCR test, sometimes requiring multiple subsequent tests to return an eventual positive result. Suggested possible reasons for this include: suboptimal clinical sampling techniques; variations in viral load; and manufacturer test kit sensitivity.¹ With surging caseloads, managing these RT-PCR 'negative' patients is proving hugely challenging.

An emerging bottleneck to effective care is dealing with isolation capacity. Inpatients who are truly PCR negative can be moved to a non-isolation ward, thereby freeing up isolation beds for COVID-19 positive patients and also reducing risk of nosocomial virus transmission. Patients with high index clinical suspicion of COVID-19, but who test negative on initial RT-PCR test, continue to be managed with respiratory isolation precautions, often undergoing repeat PCR testing. However, this means further delay while awaiting subsequent test results. Against this backdrop, an effective pathway to deal with negative COVID-19 RT-PCR results in the setting of high clinical probability is urgently needed.

A further important concern is developing regarding deisolation on patient discharge to either home or community care: a confirmed COVID-19 diagnosis - or confirmed alternative, non-COVID-19 diagnosis - is key to imparting advice to families and carers.

Imaging has been suggested as a potential solution to some of these problems.

Most patients undergo chest radiograph (CXR) at presentation to hospital, with CXRs being hot-reported using a template classification system produced by British Society of Thoracic Imaging (BSTI).² This stratifies patients into one of four groups based on CXR: COVID classic/probable; COVID indeterminate; COVID normal; and Non-COVID. Frontline doctors have found this a useful adjunct to clinical assessment.

In mainland China, CT was often a first-line investigation for COVID-19. However, such practice was burdensome on radiology departments and hugely challenging for infection control. CT in COVID-19 shows typical findings of ground glass opacity, peripheral consolidation or a combination of both. Ai et al reported CT sensitivity from their Wuhan cohort of 97% when compared with RT-PCR.³ When combined with the possibility for near instantaneous results, it is perhaps not surprising that CT has seen most widespread use in endemic regions of China, Italy and Iran. Some reports have also described typical CT findings consistent with COVID-19 in patients with initial negative RT-PCR who subsequently tested positive on repeat RT-PCR testing.^{3,4}

Several authors⁵ and professional societies⁶ have steadfastly suggested that CT should not be used as a first line or pure diagnostic test - while highly sensitive, CT findings of COVID-19 pneumonia are not specific. In addition, false negative CT rates vary in the literature, ranging from 3%-56% in RT-PCR positive patients.⁷ CT features tend to peak later (day 6-11) in the disease course.⁸ Importantly, there are huge resource implications of this approach as the scanner requires decontamination each time a 'positive' patient is scanned. Radiographers risk repeated exposures to COVID-19, with high likelihood of illness and absence from work, at a time when healthcare workers are a precious resource. Finally, concerning reports from Italy suggest that overreliance on CT potentially contributed to 'dirty' scanners acting as virus transmission vectors, thereby exacerbating COVID-19

spread among staff and COVID-19 naive patients. We agree with Hope *et al*⁵ that "...CT does not add diagnostic value" if used indiscriminately but would disagree that it has no role to play in diagnostic workup. They state "it is clear that the positive results can only be believed if the pretest probability of disease is high." This is supported by data from Wong et al where "in the scenario of high clinical suspicion of COVID-19 it is conceivable that a positive CXR can obviate the need for a CT", thereby reducing burden on CT units during the COVID-19 pandemic.⁹

While awaiting the RT-PCR result, most suspected COVID-19 patients are clinically diagnosed with the triad of clinical assessment, CXR and blood tests. CT could however play a limited, but important, role in providing diagnostic radiological confirmation in patients with clinically suspected - but RT-PCR negative - disease. This would potentially help resolve whether a patient with suspected high clinical probability of COVID-19 has an alternative diagnosis in addition to influencing infection control strategy (namely the ability to step-down a patient to a deisolation ward).

We have seen patients with negative RT-PCR at presentation with 'classic/probable' changes on CXR and repeat RT-PCR which returns positive. However, there remain a small proportion of patients in whom multiple RT-PCRs are negative and whose CXRs are repeatedly 'normal' or 'indeterminate', although clinical suspicion remains high. These 'high clinical probability' patients are those unwell enough to be admitted to hospital and are not presumed to represent the complete spectrum of COVID-19 patients, most of whom have mild symptoms requiring self-isolation in the community.

Our institution has thus devised a pragmatic protocol (figure 1), using CT to help diagnose this group of patients. Capacity for CT use in this limited way has been created as a result of cancelling elective/routine CT requests for other indications, thereby permitting not only rapid access to CT scanning but also allowing ample time for scanner terminal clean in between cases. In our algorithm, CT is performed in patients who return two negative RT-PCRs and two CXRs (≥48 hours apart) reported as 'normal' or 'indeterminate' for COVID-19 ('double-double negative'). RT-PCR remains the lynchpin of diagnosis and, if negative, is repeated (usually around 48 hours after presentation). The rationale for repeat CXR in patients where the index CXR was not COVID-19 classic/probable is that several patients go on

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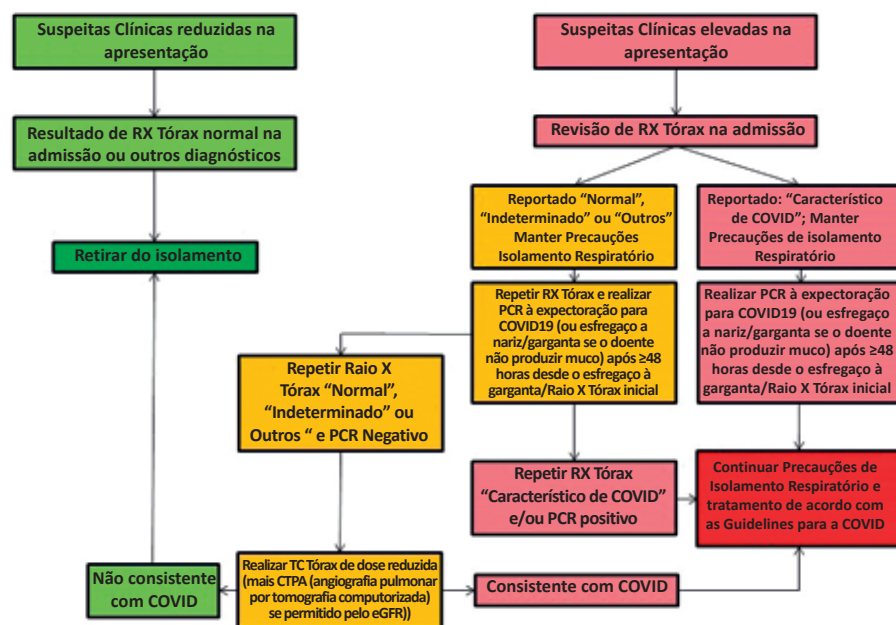


Figure 1 Proposta de controlo infeccioso de doentes internados com um RT/PCR de esfregaço do nariz ou garganta inicial negativo para COVID-19.

to develop COVID classic appearances, despite a normal/indeterminate index CXR, in the setting of high clinical probability.

Patients who are deemed eligible for CT as per our protocol undergo a sequential low dose non-contrast CT thorax and CT pulmonary angiogram (if renal function allows).¹⁰ CTPA is performed to ensure occult PE is excluded, particularly in light of reports of increased pro-thrombotic risk in COVID-19. The non-contrast CT prior is performed for two main reasons: i) dependent ground glass is often exaggerated on post-contrast scan and can be mistaken for true ground glass; ii) having a baseline non-

contrast scan can be useful if then performing subsequent unenhanced scans. The key to our pathway is thorough clinical assessment as pre-test probability determines how these patients are managed, above all else.

As the pandemic progresses it may be that so many cases 'swamp' the system that CT is forced to take a more upfront role in patient triage. At present with infection control such a key facet of patient management – as well as staff safety – the RFL NHS Trust negative PCR pathway enables a systematic approach to patient deisolation and stepdown from COVID ward to Non-COVID wards.

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Contributors SH, DC and AK devised the pathway. AT, JB, HJ, SB and AB revised the pathway, AT, SH and DC wrote the manuscript.

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ANT and AB are joint first authors.

DDC and SSH are joint senior authors.



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Impacto da proibição de fumar dentro de veículos com crianças devido a exposição fumo passivo: uma experiência natural na Inglaterra e na Escócia

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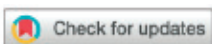
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RESUMO

A Inglaterra proibiu o fumo no interior de veículos com crianças em 2015 e a Escócia em 2016. Utilizamos dados de inquéritos de 3 anos para ambos os países ($N_{\text{Inglaterra}} = 3483-6920$, $N_{\text{Escócia}} = 232-319$) para avaliar os efeitos da proibição inglesa utilizando a regressão logística dentro de um quadro de diferenças-indiferenças. Entre as crianças de 13-15 anos de idade, os níveis de exposição regular ao fumo no interior de veículos na Escócia foram de 3,4% em 2012, 2,2% em 2014 e 1,3% em 2016 e, na Inglaterra, de 6,3%, 5,9% e 1,6%, respetivamente. A proibição em Inglaterra foi associada a uma redução absoluta (72% de redução relativa) de -4,1% (95% IC -4,9% a -3,3%) da exposição de crianças ao fumo do tabaco.

INTRODUCTION

Exposure to secondhand tobacco smoke is a significant cause of illness in children and particularly affects more disadvantaged groups.¹ Exposure of children to smoking inside cars is especially concerning owing to the very high concentrations of smoke in enclosed spaces and associations with child smoking uptake.^{2,3} Both smoking uptake and secondhand exposure to smoke are mechanisms which sustain health inequality.⁴⁻⁶

One policy response has been bans on smoking in private vehicles with children present. Evaluations of such bans are scarce and present a mixed picture.⁷⁻⁹ A ban on smoking in private vehicles with anyone aged ≤ 18 years present came into effect on 1 October 2015 in England, and on 5 December 2016 in Scotland, providing a natural experiment to evaluate policy effects.

METHOD

Data for England came from the Smoking, Drinking and Drug Use (SDDU) surveys and for Scotland from the Scottish health surveys in 2012, 2014 and 2016 (online supplementary appendix 1). We restricted the sample to children aged 13–15, as exposure for 11 and 12 year olds was reported by caregivers, which is likely to lead to under-reporting.

Our primary exposure was child-reported regular exposure to smoking inside cars, assessed, in England, with the question “In the past year, how often were you in a car with somebody smoking?” (table 1). We categorised responses of every day or most days as ‘regular exposure’. In Scotland, children were asked “Are you regularly exposed to other people’s tobacco smoke in any of these places?” (Responses: yes/no for cars/vehicles). We harmonised a measure of deprivation using free school meals and the Family Affluence Scale and include this as well as age and sex in analyses (table 1).

We used survey-weighted logistic regression to assess changes in exposure over time using a differences-in-differences analysis, which controls

for all time-invariant differences between the intervention and comparison populations.¹⁰ We considered interaction between time and country to assess changes in each country separately and with policy implementation in England in 2016. We present relative percentage changes (based on odds ratios) and absolute percentage changes (average marginal effects compared with baseline).

We conducted various additional analyses: an unadjusted model (online supplementary appendix table 2), analyses with linear trends for each country (online supplementary appendix table 3) and analyses for England only (ages 11–15), using more granular exposure data to analyse ever, monthly and regular exposure (online supplementary appendix table 4).

RESULTS

A total of 15318 responses were received in England and 822 in Scotland (online supplementary appendix 1). Self-reported regular exposure to smoke in cars was 6.3% in 2012, 5.9% in 2014 and 1.6% in 2016 for England and, respectively, 3.4%, 2.2% and 1.3% in Scotland (figure 1).

Implementation of the smoke-free policy in England was associated with an absolute reduction of -4.1% (95% CI -4.9% to -3.3%) (72% relative reduction) in the percentage of children self-reporting exposure to smoke in cars (table 2). Girls and those in the deprived group were more likely to report exposure.

Analyses unadjusted for covariates and using linear time trends were similar (online supplementary appendix tables 2 and 3). Analyses within England only, using the wider age range of 11 to 15 years, identified substantial changes in exposure in all levels of exposure assessed after implementation of the ban (online supplementary appendix table 4).

DISCUSSION

Child-reported frequency of exposure to tobacco smoke in cars fell after the 2015 introduction of the ban in England, a finding made more robust by comparison with Scotland where the policy was not introduced until the following year. This exposure remains higher in children from more deprived groups, which serves as a reminder of the socially patterned risks of smoking. These findings provide support for introducing this policy in other jurisdictions, although further evaluations are warranted. Previous research from Canadian provinces enacting such bans found more marked effects on exposure in provinces with comprehensive strategies including discouraging smoking uptake, while recent evidence has additionally pointed to exposure to smoking in cars resulting in an increase in the incidence of asthma.^{8,9} The ban is an example of the ‘Protect’ element of the MPOWER policy approach to delivering the WHO Framework Convention on Tobacco Control programme to reduce the harms caused by smoking. Importantly, the purpose of the ban is to reduce child exposure

Table 1 Key characteristics of data sources

Country	England	Scotland
Data name	Smoking Drinking Drug Use (SDDU) survey	Scottish health survey
Years and interview dates	2012: September 2012 – December 2012 2014: September 2014 – December 2014 2016: September 2016 – January 2017	2012: January 2012 – December 2012 2014: January 2014 – February 2015 2016: January 2016 – January 2017
Individuals included	2012: 4915 2014: 3483 2016: 6920	2012: 319 2014: 271 2016: 232
Age range		13–17 years
Exposure to tobacco smoke in cars question	2012: Two separate questions: "In the past year, how often were you in your family's car (OR) someone else's car with somebody smoking?" (Responses: every day or most days; once or twice a week; once or twice a month; less often than once a month; never in the past year; don't know) 2014 and 2016: In the past year, how often were you in a car with somebody smoking? This could be your family's car or someone else's car. (Responses: every day or most days; once or twice a week; once or twice a month; less often than once a month; never in the past year; don't know) In this study 'every day or most days' classed as 'regular exposure'	2012–2016: "Are you regularly exposed to other people's tobacco smoke in any of these places?" (responses: yes/no for in cars/vehicles, etc)
Deprivation marker	2012 and 2014: Child reported receipt of free school meals (FSM) 2016: Family Affluence Scale (low, middle, high). Harmonised so low group equivalent to receiving FSM	2012–2016: Scottish index of multiple deprivation in five groups Harmonised so most deprived group comparable to receiving FSM or being in lowest affluence band

to tobacco smoke, for which this study provides evidence, and not to drive prosecutions (eg, coverage presenting the legislation as a failure due to the low number of arrests <https://www.mirror.co.uk/news/uk-news/car-smoking-ban-massive-flop-10858407>).

Strengths and limitations

The strength of this experiment using high-quality data from Scotland and England is that the design permits observed changes to be plausibly ascribed to the policy intervention. However, differences in the data used between countries deserve consideration. Different measurements of exposure in England and Scotland mean that we cannot directly compare exposure levels between countries, and the measure of deprivation we use has been harmonised from measures which have not previously been combined. However, analyses of data for England alone, using different levels of exposure, and not including the deprivation measure, all produced concordant results. Combining data sources also meant that we could employ a difference-in-difference design, which controls for time-invariant differences between countries and provides stronger evidence than relying on England alone. Exposure was based on self-report only, and reporting bias might have changed over time, although this would probably have been similar in both countries. Interview dates were not available for the Scottish data, and sampling in 2016 included almost 2 months after the introduction of their ban. Misclassification from sampling dates would probably bias associations towards the null point, but the direction of any biases due to harmonising data sources is difficult to predict. Reported frequencies of exposure frequency in Scotland were low, meaning that there might have been some floor effects and, as these analyses use only three data points from each country, future analyses with more data are recommended and may provide discrepant results.

CONCLUSIONS

Our results suggest that banning smoking in private vehicles carrying children has been successful in its main aim of reducing their

exposure to tobacco smoke. Given children's known vulnerability to secondhand smoke, reductions in exposure will probably result in improved health.

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Contributors AAL, CM and NSH conceived the study idea. Analyses were by AAL with TH. All authors provided intellectual input to the interpretation of results and approved the final manuscript.

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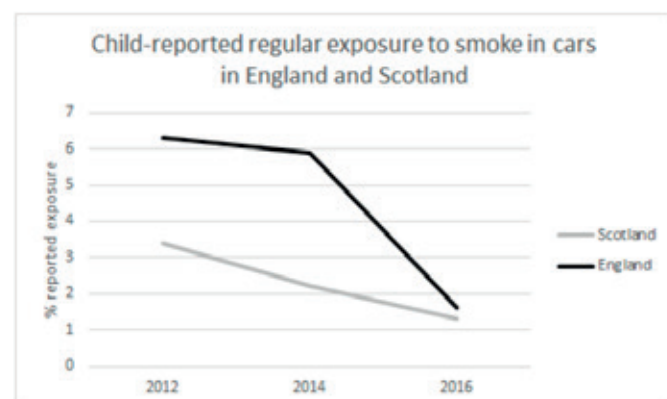
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Table 2 Results from logistic regression difference in difference analyses of impact of policy implementation on self-reported exposure to smoking in vehicles

	AOR (95%CI)	Absolute % difference (95%CI)
Scotland 2012–2014	0.34 (0.15 to 0.80)	–0.45 (–2.70 to 1.80)
Scotland 2014–2016	0.25 (0.07 to 0.79)	0.00 (–1.05 to 1.06)
England 2012–2014	1.00 (0.82 to 1.22)	–1.04 (–3.34 to 1.27)
England 2014–2016 (policy implementation)	0.28 (0.21 to 0.37)	–4.11 (–4.91 to –3.31)
Age 13 years	ref	ref
Age 14 years	1.01 (0.80 to 1.28)	0.04 (–0.77 to 0.84)
Age 15 years	1.22 (0.99 to 1.51)	0.74 (–0.05 to 1.53)
Boys	ref	ref
Girls	1.61 (1.34 to 1.93)	1.75 (1.07 to 2.43)
Not deprived group	ref	ref
6* Not deprived group	1.98 (0.82 to 1.21)	2.53 (1.76 to 3.29)

Absolute % differences derived from marginal effect compared with baseline.

AOR, adjusted odds ratio.

**Figure 1** Percentages of child-reported regular exposure to smoke in cars in England and Scotland 2012–2016.

A admissão hospitalar no Reino Unido durante o fim-de-semana não influencia o prognóstico de adultos com pneumonia adquirida na comunidade

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RESUMO

Os resultados para adultos com pneumonia adquirida na comunidade (PAC) admitidos em hospital durante o fim-de-semana foram comparados com os admitidos durante os dias de semana, utilizando dados das auditorias nacionais de PAC da Sociedade Torácica Britânica. De 31 400 casos, 40,7% corresponderam a internamentos de fim-de-semana. Estes doentes eram mais velhos (idade média 72 vs. 71,3 anos, $p=0,001$) e mais suscetíveis a PAC de maior gravidade (28,9% vs. 27,1%, tendência $p=0,003$), mas apresentaram uma mortalidade hospitalar ajustada a 30 dias ligeiramente inferior (OR ajustado 0,94 95% IC 0,88 a 1,01) em comparação com os admitidos durante os dias de semana. Mais doentes no grupo de fim-de-semana receberam antibióticos nas 4 horas seguintes à admissão (70,3% vs. 68,7%, OR ajustado 1,07 95% IC 1,01 a 1,12). Não observámos um aumento da mortalidade dos adultos admitidos ao fim-de-semana com PAC.

INTRODUCTION

The 'weekend effect', an increased risk of mortality for patients admitted on a Saturday or Sunday compared with a weekday, has garnered attention since 2001. Studies have provided evidence for it in differing healthcare systems, although causes remain unclear and evidence for a correlation between intensity of specialist hospital staffing and weekend mortality is lacking.^{1,2}

Community-acquired pneumonia (CAP) remains a common reason for emergency medical admission in the UK and carries a high mortality of 10%–15%.³ Unlike some acute emergency conditions that require rapid access to specialist services, the optimal management of CAP, as described in guideline recommendations, can be delivered by acute medical staff of varying grades.^{3,4} As such, clinical outcomes are not expected to be influenced by weekend admission. Our aim was to assess whether outcomes and processes of care for CAP differ between adults admitted at the weekend compared with the weekday.

METHODS

Aggregate data from six British Thoracic Society national adult CAP audits (winters 2009/10, 10/11, 11/12, 12/13, 14/15, 18/19) including cases as defined in previous work were used.⁵ Cases were identified by participating institutions via ICD10 codes mapping to a primary discharge diagnosis of pneumonia (J12.0–J18.0) and selected for eligibility against inclusion criteria to confirm a clinical and radiographic diagnosis of CAP. The primary outcome of interest was 30-day inpatient mortality. Secondary outcomes included 7-day and 3-day inpatient mortality, time to discharge in days, critical care admission and readmission within 30 days of discharge. Process of care measures analysed were CXR and receipt of antibiotics within 4 hours of admission, use of guideline concordant antibiotics and time to senior review.

The cohort was divided into two groups based on time and date of first presentation to hospital. Definitions for out-of-hours are taken from the NHS services website:⁶ weekday was defined as 08:00 Monday to 18:29 Friday; weekend was defined as 18:30 Friday to 07:59 Monday. Patients admitted on a holiday (defined as 18:30 on the day prior to 07:59 on the next working day) were included in the weekend group.

Descriptive statistics were used for group comparison and adjusted ORs calculated using a mixed-effects multivariate logistic regression models for each outcome variable. Following review of published literature, minimum sufficient adjustment variable sets were defined using directed acyclic graphs.⁷ The adjustment set for mortality included age, binary constituent parts of the CURB65 score, presence or absence of comorbidities and admitting hospital as a random effect. Analysis of time to discharge was performed using a competing risks analysis to obtain a HR for discharge within 30 days. Inpatient death was treated as a competing event. Patients who remained an inpatient at 30 days were censored from the analysis at this time point.

Cases were excluded from the analysis if the time of admission, primary outcome or variables within the minimal adjustment set were missing (<7% of data from each variable). All statistical analyses were performed using STATA 15.

RESULTS

Of 34194 cases, those missing key data (admission time ($n=1008$), status on discharge ($n=193$) and age ($n=683$)) were excluded leaving 32984 for descriptive analysis. Patients who presented at the weekend (40.7%) were older (72 vs 71.3 years; OR 1.002), more likely to reside in a care home (14.8% vs 12.8%; OR 1.13), be admitted via the emergency department (84.8% vs 73.2%; OR 2.04) and have high severity pneumonia than those admitted during weekdays (table 1).

Of 31400 cases with available data for multivariate analysis of the primary outcome, adjusted mortality in the weekend group was slightly lower at 30 days (15.4% vs 15.5%; aOR 0.94, 95%CI 0.88 to 1.01) and 7 days (10.3% vs 10.4%; aOR 0.95, 95%CI 0.87 to 1.03) but equal at 3 days (6.2% vs 6.2%; aOR 0.96, 95%CI 0.87 to 1.06). No differences were found in rates of critical care admission (6% vs 5.8%; aOR 1.05, 95%CI 0.95 to 1.16) or readmission within 30 days of discharge (12.9% vs 13.1%; aOR 0.99, 95%CI 0.92 to 1.07). Results for each outcome were similar when analysed by severity category (results available on request).

Patients admitted at the weekend had a 2% higher probability of discharge at any point from admission to 30 days than the weekday group (adjusted Hazards Ratio 1.02 95%CI 1.00 to 1.05, $p=0.05$). Patients admitted at weekends were more likely to receive antibiotics within 4 hours (70.3% vs 68.7%; aOR 1.07, 95%CI 1.01 to 1.12), but less likely to be reviewed by a senior clinician within 12 hours of



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Table 1 Population characteristics by cohort group—weekday vs weekend admissions

ID	Weekday admissions n (%)	Weekend admissions n (%)	P value
Number of patients	19 552 (59.5)	13 432 (40.7)	
Demographics			
Age (mean)	71.3	72	0.001
Gender (male)	9353 (47.8)	6506 (48.4)	0.28
Usual residence care home	2493 (12.7)	1992 (14.8)	0.0002
Severity by CURB65 category			
Low (Score 0–1)	8017 (43.0)	5333 (41.7)	
Moderate (Score 2)	5558 (29.9)	3753 (29.4)	
High (Score 3–5)	5053 (27.1)	3686 (28.9)	0.003 (trend)
Admitted via ED (%)	14 012 (73.2)	11 146 (84.8)	<0.0001
Admitted overnight (%)	6431 (32.9)	6947 (51.7)	<0.0001
Comorbidity present			
Cardiac failure	1726 (8.8)	1179 (8.8)	0.95
Other chronic heart disease (excluding hypertension)	4578 (23.4)	3112 (23.2)	0.57
Cerebrovascular disease	1853 (9.5)	1398 (10.4)	0.005
Liver disease	236 (1.2)	160 (1.2)	0.83
Chronic kidney disease	1741 (8.9)	1007 (7.5)	<0.0001
Malignancy	1503 (7.7)	948 (7.1)	0.004
Chronic obstructive pulmonary	4626 (23.7)	3053 (22.7)	0.05
Other chronic lung disease	2667 (13.7)	1752 (13.0)	0.89
Diabetes	2392 (12.2)	1738 (12.9)	0.06
Dementia	1557 (8.0)	1229 (9.2)	0.02

Population characteristics in the weekday and weekend groups are presented as number, % and p-values. P-values of <0.05 are displayed in bold.
ED, emergency department.

admission (71.7% vs 74.7%; aOR 0.85, 95%CI 0.80 to 0.89). There were no differences in performance of CXR within 4 hours (85.9% vs 86%; aOR 1.01, 95%CI 0.94 to 1.08) or use of guideline concordant antibiotics (57.6% vs 57%; aOR 0.99, 95%CI 0.94 to 1.04) (table 2).

DISCUSSION

Our main finding is that 30-day inpatient mortality, adjusted for disease severity and comorbidities, was slightly lower for adults admitted to hospital with CAP at weekends compared with weekdays. This is in contrast to published evidence on the ‘weekend effect’, much of which is not disease-specific. Evidence related to pneumonia is mixed. In Japan, Uematsu et al found a 10% higher adjusted total inpatient mortality for weekend admissions with severe pneumonia.⁸ In Australia, Baldwin et al found no association between day of week admitted and mortality.⁹

In England, analysis of administrative inpatient data linked to mortality data from 2004 to 2012 found marginally increased mortality for patients with pneumonia presenting at the weekend (aOR 1.037, 95%CI 1.035 to 1.049).¹⁰ Unlike administrative datasets, our study cohort comprised cases with radiologically confirmed

med CAP together with data on co-morbidity and severity of CAP on admission, thus reducing misclassification bias (from inclusion of patients without CAP) and allowing for appropriate case-mix adjustment. These features may explain the difference of our findings to previous studies. The slightly lower adjusted mortality in the weekend group may reflect more rapid access to time-critical aspects of care, as evidenced by increased access to antibiotics within 4 hours of admission.

A limitation of this study is a lack of microbiological data. A higher proportion of antibiotic-resistant, or more virulent, pathogens within the sicker weekend group, compared with the weekday group, cannot be excluded. If present, the direction of bias would be towards a higher weekend mortality and would mean the study findings are conservative. In this analysis, we did not adjust for vaccination status due to the unavailability of robust vaccination data. In the UK, priority groups for influenza and pneumococcal vaccination are identified according to older age and presence of comorbid illnesses. Overall, there were no major baseline differences between the two groups that would suggest a large difference in relation to eligibility for vaccination although we cannot exclude the possibility that vaccine uptake may have been higher in one of the groups.

We found no evidence of increased mortality for adults admitted at the weekend with CAP despite these patients being older and having higher severity pneumonia than patients admitted at weekdays. These results are reassuring and do not support a need for special ‘weekend measures’ in the management of CAP.

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Collaborators To ensure members/collaborators of “British Thoracic Society” are citable in PubMed please ensure individuals are listed in the ‘Collaborators’ section. **Contributors** HL, WSL and TM provided the analysis for the draft paper. All authors were involved in drafting and approving the final paper for publication.

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Table 2 Outcomes and process of care measures in the weekend and weekday groups

	Weekday admissions n (%)	Weekend admissions n (%)	or (95%CI)	Adjusted or* (95%CI)	P value
Outcomes					
Inpatient death within 30 days	3037 (15.5)	2062 (15.4)	0.99 (0.93 to 1.05)	0.94 (0.88 to 1.01)	0.08
Inpatient death within 7 days	2027 (10.4)	1380 (10.3)	0.99 (0.92 to 1.06)	0.95 (0.87 to 1.03)	0.19
Inpatient death within 3 days	1210 (6.2)	835 (6.2)	1 (0.92 to 1.10)	0.96 (0.87 to 1.06)	0.41
Critical care admission	5 (3–9)	5 (3–10)			0.23
Median LOS (IQR)	1110 (5.8)	789 (6.0)	1.04 (0.95 to 1.14)	1.05 (0.95 to 1.16)	0.32
Readmission within 30 days of discharge	2054 (13.1)	1402 (12.9)	0.99 (0.92 to 1.06)	0.99 (0.92 to 1.07)	0.89
Process of care measures					
Senior review within 12 hours	13409 (74.7)	8797 (71.7)	0.86 (0.81 to 0.90)	0.85 (0.80 to 0.89)	<0.0001
CXR within 4 hours	15 544 (86.0)	10 763 (85.9)	0.99 (0.93 to 1.06)	1.01 (0.94 to 1.08)	0.77
Antibiotics within 4 hours	11 713 (68.7)	8296 (70.3)	1.08 (1.02 to 1.13)	1.07 (1.01 to 1.12)	0.02
Guideline concordant antibiotics:	10 740 (57.0)	7480 (57.6)	1.03 (0.98 to 1.07)	0.99 (0.94 to 1.04)	0.80

Unadjusted Odds Ratios, adjusted ORs (aOR) and p values are presented. The baseline group for comparison is the weekday admission group. P-values <0.05 are displayed in bold.

*All outcomes are adjusted for age, CURB65 score constituents (except age), cardiac failure, other chronic heart disease (excluding hypertension), cerebrovascular disease, liver disease, chronic kidney disease, malignancy, COPD, other chronic lung disease, diabetes, dementia and hospital of admission.

CXR, chest radiograph; LOS, length of stay in days.

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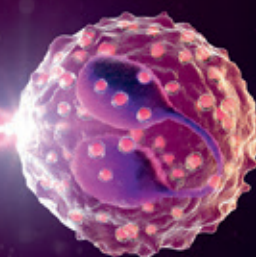


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*Caneta pré-cheia.

1. Ferguson et al., "Single-Use Autoinjector Functionality And Reliability For At-Home Administration Of Benralizumab For Patients With Severe Asthma: GRECO Trial Results", Journal of Asthma and Allergy 2019;12 363–373;
2. RCM de Fasenra consultado a 24/07/2020 em www.infarmed.pt.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaooram> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel: +351 21 798 73 73; Linha do medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Fasenra 30 mg solução injetável em caneta pré-cheia.** Cada caneta pré-cheia contém 30 mg de benralizumab* em 1 ml. *Benralizumab é um anticorpo monoclonal humanizado produzido por tecnologia de ADN recombinante em células ovárias do hamster chinês. Solução injetável em caneta pré-cheia (injetável) (Fasenra Pen). Solução clara a opalescente, incolor a amarela e pode conter partículas translúcidas ou brancas a esbranquiçadas. **Indicações terapêuticas:** Fasenra é indicado como tratamento adjuvante de manutenção em doentes adultos com asma eosinofílica grave, inadequadamente controlada apesar das doses elevadas de corticosteroides inalados em associação a agonistas-β de longa duração de ação. **Posologia e modo de administração:** O tratamento com Fasenra deve ser iniciado por um médico com experiência no diagnóstico e tratamento da asma grave. Após o treino adequado da técnica de injeção subcutânea e educação sobre sinais e sintomas de reações de hipersensibilidade, os doentes sem história conhecida de ocorrência de anafilaxia, ou os seus cuidadores, podem administrar Fasenra se o seu médico considerar apropriado, com seguimento médico se necessário. A autoadministração só deve ser considerada em doentes tratados anteriormente com Fasenra. **Posologia:** A dose recomendada de benralizumab é 30 mg administrados por injeção subcutânea a cada 4 semanas para as primeiras 3 doses, e depois a cada 8 semanas. Se uma injeção não for administrada na data planeada, a dose deve ser administrada assim que possível de acordo com o regime indicado; não deve ser administrada uma dose a duplicar. Fasenra destina-se ao tratamento de longa duração. A decisão de continuar a terapêutica deve ser efetuada pelo menos uma vez por ano, com base na severidade da doença, no nível de controlo das exacerbações e na contagem sanguínea de eosinófilos. Não é necessário qualquer ajuste de dose em doentes idosos ou em doentes com compromisso da função renal ou hepática. **População pediátrica:** A segurança e eficácia de Fasenra em crianças com 6 a 18 anos de idade não foram estabelecidas. Não estão disponíveis dados em crianças com 6 a 11 anos de idade. Os dados atualmente disponíveis em crianças com 12 a 18 anos de idade encontram-se descritos nas secções 4.8, 5.1 e 5.2 do RCM mas não pode ser feita qualquer recomendação posológica. **Modo de administração:** Fasenra é administrado por injeção subcutânea. Deve ser injetado na coxa ou abdómen. Se o profissional de saúde ou o cuidador administrar a injeção, esta pode ser efetuada na parte superior do braço. Não deve ser injetado em áreas onde a pele está sensível, ferida, eritematosa ou endurecida. **Contraindicações:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Fasenra não deve ser utilizado para tratar exacerbações agudas da asma. Os doentes devem ser informados a procurar aconselhamento médico se a sua asma permanecer não controlada ou se agravar após o início do tratamento. A descontinuação abrupta de corticosteroides após o início do tratamento com Fasenra não é recomendada. Se necessário, a redução das doses de corticosteroides deve ser gradual e efetuada sob supervisão de um médico. **Reações de hipersensibilidade:** Após a administração de benralizumab ocorreram reações sistémicas agudas, incluindo reações anafiláticas e reações de hipersensibilidade (por exemplo, urticária, urticária papular, erupção cutânea). Estas reações podem ocorrer horas após a administração, mas em alguns casos tiveram um início tardio (i.e. dias). História de anafilaxia não relacionada com benralizumab pode ser um fator de risco para a ocorrência de anafilaxia após a administração de Fasenra. Os doentes devem ser monitorizados por um período de tempo adequado após a administração de Fasenra, de acordo com a prática clínica. Em caso de reação de hipersensibilidade, Fasenra deve ser descontinuado permanentemente e deve ser iniciado o tratamento adequado. **Infeção parasitária (Helmínica):** Os eosinófilos podem estar envolvidos na resposta imunitária a algumas infeções helmínticas. Os doentes com infeções helmínticas conhecidas foram excluídos da participação nos ensaios clínicos. Desconhece-se se Fasenra pode influenciar uma resposta do doente contra infeções helmínticas. Os doentes com infeções helmínticas pré-existent devem ser tratados antes de iniciar o tratamento com Fasenra. Se os doentes ficarem infetados durante o tratamento com Fasenra e não responderem ao tratamento anti-helmínico, o tratamento com Fasenra deve ser descontinuado até a infeção se resolver. **Interações medicamentosas e outras formas de interação:** Em doentes com idades compreendidas entre 12 e 21 anos com asma grave, a resposta humoral induzida pela vacinação contra o vírus da gripe sazonal não parece ser afetada pelo tratamento com benralizumab. Não é esperado um efeito de benralizumab na farmacocinética de medicamentos administrados concomitantemente. As enzimas do citocromo P450, bombas de efluxo e os mecanismos de ligação a proteínas não estão envolvidos na depuração de benralizumab. Não existe evidência da expressão de IL-5Rα nos hepatócitos. A depleção de eosinófilos não produz alterações sistémicas crónicas das citocinas pró-inflamatórias. **Efeitos indesejáveis:** **Frequentes:** Faringite, Reações de hipersensibilidade, Cefaleia, Pirexia, Reação no local de injeção; **Desconhecida:** Reação anafilática. **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** AstraZeneca Produtos Farmacêuticos, Lda., Rua Humberto Madeira, 7, Queluz de Baixo, 2730-097 Barcarena. Informações revistas em julho de 2020. **Para mais informações deverá contactar o representante local do titular da Autorização de Introdução no Mercado. Medicamento de receita médica restrita, de utilização reservada a certos meios especializados. Financiada no âmbito da avaliação prévia à utilização hospitalar. Versão 1.0 (julho 2020).**

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