

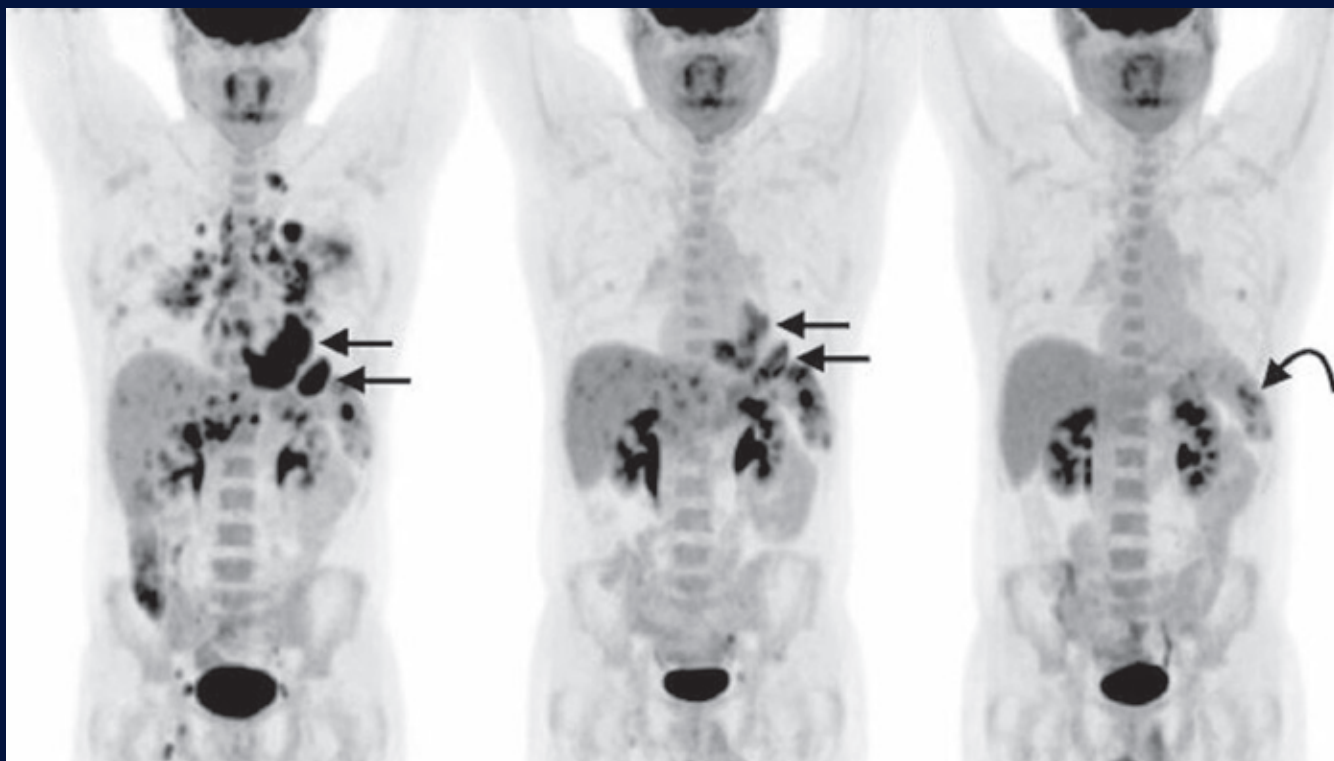
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Editorial

Estamos a chegar ao fim do mês de maio e os números da pandemia por SARS CoV-2 estão finalmente em níveis mais toleráveis que, conjugados com o crescente número de pessoas residentes em Portugal que já receberam, pelo menos, uma dose de vacina, e ao número não negligenciável de pessoas que contraíram infeção, nos pode dar alguma esperança de, dentro de pouco tempo, conseguirmos atingir uma imunidade populacional que nos permita regressar a uma certa “normalidade” semelhante à que se vivia no período pré pandémico.

Tudo isto, se conseguirmos manter comportamentos de socialização aceitáveis sem relaxar as precauções de contágio, se a chegada tão desejada dos turistas não trazer consigo novas variantes para as quais as pessoas imunizadas já não estejam protegidas, se conseguirmos que as populações mais desfavorecidas dos Países de baixo e médio rendimento tenham acesso à vacinação e se não houver abrandamento da vigilância sanitária por fadiga ou diminuição de recursos dos profissionais, entre outras, muitas outras coisas que podem ainda correr mal.

A pandemia trouxe uma das maiores, se não a maior, alteração no quotidiano das pessoas das últimas décadas com um enorme impacto do ponto de vista sanitário, económico, social e psicológico. Muitos comentadores e sociólogos, dizem que a nossa vida nunca mais será a mesma depois da pandemia. Sim, é verdade, mas é igualmente muito importante que sejamos capazes, individual e coletivamente, de extrair as devidas lições dos acontecimentos destes dois últimos anos.

Ao nível da capacidade de prestação de cuidados de saúde, o impacto foi brutal. A mobilização da atenção dos profissionais de saúde para os cuidados prioritários a pessoas com Covid-19, o acompanhamento das pessoas infetadas na comunidade e o rastreio, identificação e acompanhamento dos contactos, provocaram um adiamento sem precedentes nos atos médicos e de saúde realizados nos últimos meses. Apesar da retoma que já se começa a fazer sentir, os atrasos de cirurgias, consultas, tratamentos, atos de diagnóstico, acompanhamento de doentes crónicos e rastreios populacionais estão já a causar um impacto considerável na saúde dos cidadãos e a situação poderá, a prazo, ser ainda mais grave, à medida que se tornem aparentes as consequências dos referidos atrasos e adiamentos.

Apesar do contexto desfavorável, a formação profissional tem-se mantido muito ativa, não só em relação aos temas específicos relacionados com as novas competências necessárias para lidar com a pandemia, como também dando continuidade às atividades de partilha de conhecimentos e de inovação científica através dos congressos e conferências que fazem parte do calendário habitual, nos últimos tempos convertidos em eventos em formato virtual ou híbrido e que começam lentamente a procurar regressar ao formato presencial. Este ano, prevê-se já que alguns dos eventos voltem a acontecer em formato presencial, mesmo que em simultâneo com a participação a distância.

Também em relação à produção e divulgação de artigos e publicações, a comunidade científica não esteve parada. Para além da inevitável e profusa produção científica de artigos relacionados com Covid-19, continuaram a ser publicados muitos estudos sobre outros temas que interessam certamente aos profissionais de saúde.

É o caso das Revistas *Thorax* e *Archives of Disease in Childhood* que nos proporcionam periodicamente uma vasta e interessante oferta de temas. Assim, voltamos com um novo número da edição em língua Portuguesa de artigos dessas revistas em que, para além da Covid-19, se abordam outros temas relevantes como poluição atmosférica e bronquiolite infantil, apneia obstrutiva do sono, risco de osteoporose devido a corticosteroides em pessoas com asma e hesitação vacinal.

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

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COVID-19 e o que acontece a seguir ?

Nicholas S Hopkinson,¹ Gisli Jenkins,² Nicholas Hart³

No final de janeiro de 2020, a OMS declarou o surto de SARS-CoV-2 uma emergência de saúde pública a nível internacional, o seu nível de alarme mais elevado. Embora as medidas no Reino Unido para reduzir a propagação e “proteger o SNS” tenham impedido um colapso completo do sistema de saúde, o atraso na implementação de um confinamento até 23 de março fez com que ocorressem dezenas de milhares de mortes adicionais e, até dezembro, mais de 220.000 hospitalizações por COVID-19, com efeitos que, para muitos indivíduos, continuaram a persistir após a alta hospitalar. (<https://coronavirus.data.gov.uk/healthcare>).¹⁻⁵

O SARS-CoV-2 visa o epitélio respiratório e tem uma multiplicidade de consequências clínicas que vão desde a doença assintomática, ligeira, a moderada e grave. Embora a doença, no seu início, provoque principalmente sintomas respiratórios, muitos doentes terão uma incapacidade física, cognitiva e psicológica que exigirá uma gestão a longo prazo. Nesta edição da *Thorax* com artigos do *Archives of Disease in Childhood*, edição portuguesa nas breves comunicações, temos do Reino Unido, descrições sobre o resultado de curto a médio prazo após a alta de doentes hospitalizados com COVID-19, identificando um padrão de cinco sintomas principais persistentes: falta de ar, tosse, fadiga, dores musculares/articulares e má qualidade do sono.⁶⁻⁹ Mandal *et al* recrutaram 384 doentes de três grandes hospitais londrinos.⁶ Numa mediana de 54 dias após a alta hospitalar, cerca de metade dos doentes relataram falta de ar persistente e um terço relatou tosse persistente. Dois terços dos doentes descreveram fadiga persistente e má qualidade do sono, com 15% a relatar resultados consistentes com depressão. Os biomarcadores de inflamação contínua (D-dímero e CRP) foram frequentemente elevados.

Apenas 11% dos doentes reportaram uma ausência de todos estes quatro sintomas principais. É de salientar que, embora a doença respiratória fosse uma comorbilidade comum em doentes hos-

pitalizados, a pontuação na escala de Dispneia MRC no seguimento não foi diferente entre os doentes com e sem doença respiratória pré-existente [ambas medianas (IQR) 2 (1-3)]. Num estudo realizado por Hall *et al* em Londres,⁷ os investigadores consultaram os doentes por telefone antes da consulta clínica presencial e relataram que um terço dos doentes teria retomado o seu nível funcional inicial e que recusaram a consulta clínica, um terço foi considerado não egível para consulta presencial devido ao seu estado clínico ou estava incontactável e um terço apresentava sintomas persistentes. Embora a falta de ar fosse uma característica proeminente nos 200 indivíduos com sintomas persistentes, com uma pontuação mediana MRC de 2,6±1,2, 31% dos doentes não necessitaram de oxigénio na fase aguda da doença durante o internamento. Dos 170 doentes submetidos a teste de marcha de 6 minutos, um terço registou dessaturação de oxigénio superior a 4%, 27% apresentou uma redução do volume pulmonar e 44 % uma redução na transferência gasosa. Foram observadas anomalias radiológicas persistentes nos exames imagiológicos do tórax em um terço dos doentes seguidos.

Em outro estudo, Arnold *et al* no relatório de Bristol⁸ informam o seguimento de 110 doentes numa mediana de 83 dias após a sua admissão hospitalar. Neste estudo, quase três quartos dos doentes reportaram pelo menos um sintoma persistente, com 39% a descrever falta de ar, 39% fadiga e 24% insónias. Os sintomas persistentes foram mais comuns nos doentes que apresentavam uma doença inicial mais grave. É importante salientar que, mesmo no grupo que não requereu oxigénio suplementar durante a admissão, 26% relatou falta de ar e fadiga contínua com má qualidade de sono.

Em Vancouver, Shah *et al*⁹ realizaram um estudo prospetivo pós-alta hospitalar em 60 doentes examinados 12 semanas após o início dos sintomas. As anomalias da função pulmonar foram comuns, com uma redução da transferência gasosa em 52% e uma redução da capacidade pulmonar total em 45%. As alterações persistentes observadas na TAC foram praticamente universais: 83% dos doentes apresentaram áreas de vidro fosco e 65% áreas de reticulação, enquanto apenas 12% não apresentaram qualquer anomalia nos resultados imagiológicos. Verificou-se uma forte associação entre os dias de suplementação de oxigénio durante a fase

aguda da COVID-19, tanto na redução da transferência de gás como nas anomalias de TC no seguimento. Não obstante, apenas 20% dos participantes relataram falta de ar persistente. Estes dados observacionais realçam a necessidade de um acompanhamento sistemático nesta população de doentes,¹⁰ mas são necessários mais estudos para determinar ao pormenor a natureza e os mecanismos das sequelas da infeção por SARS-CoV-2 a nível pulmonar, sistémico e psicológico. Uma proporção substancial de doentes hospitalizados apresenta alterações radiológicas ou fisiológicas consistentes com anomalias intersticiais, havendo uma necessidade urgente de definir a trajetória desta patologia pulmonar. Independentemente de estas mudanças permitirem progressos ou resoluções, elas terão um impacto profundo nos cuidados de saúde nos próximos anos.

Os estudos de longo prazo também devem investigar o efeito da perturbação do eixo do cérebro-coração-rim-músculo esquelético com o desenvolvimento de imagens fisiológicas e incluir impactos físicos e psicológicos para que possamos desenvolver estratégias clínicas para gerir a perturbação de stress pós-traumático e outras morbilidades psicológicas. Curiosamente, o único estudo sobre défice cognitivo⁷ determinou que o teste utilizado seria inadequado para esta coorte de doentes. Será importante assegurar que são utilizadas ferramentas apropriadas para esta área crucial de avaliação. O estudo multicêntrico PHOSPCOVID (www.phosp.org/), que irá recrutar 10000 doentes hospitalizados por COVID-19 em todo o Reino Unido, é um exemplo desta abordagem abrangente, incorporando áreas de investigação física, psicológica e cognitiva. Ao longo de 12 meses, as avaliações fornecerão dados mecanicistas e de observação clínica sobre a trajetória de recuperação dos doentes após hospitalização por COVID-19, a fim de proporcionar um maior conhecimento do impacto a longo prazo na sua saúde.

O trabalho descrito até à data em doentes hospitalizados exclui dois grupos importantes. O primeiro são os indivíduos infetados com SARS-CoV-2 e que apresentaram uma doença moderada a grave, mas que evitaram a hospitalização, e o segundo são os indivíduos com “COVID-19 de Longa Duração” que apresentaram sintomas debilitantes persistentes após o que pode ter sido, em termos comparativos, uma fase ligeiramente aguda.⁴ Os resultados a longo prazo nas diferentes populações são suscetíveis a variações. Portanto, entre os participantes no estudo Zoe Symptom,¹¹ nos 4182 casos de COVID-19 com teste positivo para SARS-CoV-2 por PCR e que registaram os seus sintomas prospetivamente, 13,9%

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apresentaram-se no hospital por causa de COVID-19, 13,3% apresentavam sintomas com uma duração >28 dias, 4,5% com uma duração >8 semanas e 2,3% com uma duração >12 semanas.¹² 43,9% das pessoas com sintomas às 8 semanas apresentaram-se no hospital. Stavem *et al*¹³ estudaram os sintomas e os seus determinantes 1,5-6 meses após o aparecimento dos sintomas numa população norueguesa não hospitalizada com COVID-19 confirmada. Cinquenta e três por cento das mulheres e 67% dos homens estavam sem sintomas, enquanto 16% reportaram dispneia, 12% perda/perturbação do olfato e 10% perda/perturbação do paladar. Uma maior carga de sintomas durante a doença inicial foi associada a uma maior carga de sintomas no seguimento, sugerindo uma correlação com a gravidade da doença.

Dada a persistência de sintomas como falta de ar, tosse, fadiga, dores musculares e articulares e má qualidade de sono após a COVID-19, existe a necessidade de uma abordagem de reabilitação para atender às questões físicas e psicológicas de forma holística e a orientação da British Thoracic Society está disponível no seu website (www.brit-thoracic.org.uk). A abordagem estruturada de auto-gestão que se tem mostrado eficaz no tratamento da síndrome pós-poliomielite também pode fornecer um modelo para o efeito.¹⁴ A pontuação no teste de avaliação de DPOC, uma medida estabelecida para avaliar a resposta à reabilitação pulmonar, foi reformulada para servir de ferramenta para a avaliação dos sintomas pós-COVID.¹⁵

Inclusivamente antes da COVID-19, a prestação de serviços de reabilitação pulmonar para apoiar pessoas limitadas pela falta de ar era inadequada para satisfazer o nível de necessidade¹⁶ e a pandemia em curso limitou ainda mais a capacidade de prestação de serviços pessoalmente. As pessoas com doenças de longo prazo clinicamente vulneráveis à COVID-19 foram aconselhadas

a praticar um isolamento social rigoroso e também sofreram dificuldades no seu acesso aos cuidados de saúde.^{17,18} A pandemia acentuou as desigualdades e o racismo estrutural nos cuidados de saúde.¹⁹ Esperamos que a compreensão e o reconhecimento das necessidades das pessoas que recuperam da doença conduza, por sua vez, a uma maior sensibilização para a importância da reabilitação em todo o sistema de cuidados de saúde.

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Temperatura ambiente, poluição atmosférica e bronquiolite infantil

Holly Ching Yu Lam,¹ Shakoor Hajat²

A bronquiolite aguda é uma das principais causas de hospitalizações relacionadas com infecções respiratórias do trato inferior entre crianças pequenas, sendo frequentemente atribuída à infecção por vírus sincicial respiratório (VSR). A sazonalidade da infecção por VSR tem sido relatada em diferentes regiões climáticas, com uma maior incidência no Inverno em regiões de clima temperado e na estação das chuvas em áreas mais próximas do equador.¹ As exposições ao meio ambiente, tais como fatores meteorológicos e poluentes atmosféricos, que afetam a suscetibilidade do hospedeiro, a sobrevivência do agente patogénico e a transmissão podem, em parte, conduzir à sazonalidade da bronquiolite aguda, mas estas têm sido menos investigadas comparativamente a outras condições respiratórias infantis comuns, como é o caso da asma. Em regiões subtropicais, a sazonalidade na bronquiolite aguda infantil tem sido relatada por vários estudos, mas poucos investigaram a sua relação com a exposição ambiental.

O relatório nesta edição de Leung *et al* começa por preencher algumas destas lacunas.² Num estudo bem conduzido de regressão com séries temporais, investigou-se a associação de fatores meteorológicos e poluentes atmosféricos no quotidiano das crianças (≤ 2 anos de idade), hospitalizações de bronquiolite aguda durante um período de 10 anos no cenário subtropical metropolitano de Hong Kong. O estudo analisou dados de 12 hospitais públicos e considerou cuidadosamente os efeitos retardados de cada exposição, embora não tenham sido apresentados possíveis efeitos sinérgicos. Considerando que estudos de outras regiões mostram picos singulares na incidência anual de bronquiolite e VSR no Inverno ou na estação das chuvas,^{1,3} este estudo sugere dois picos na incidência de bronquiolite em Hong Kong - um maior na Primavera e um menor no final do Verão.²

Após o ajustamento sazonal, verificou-se um maior risco de hospitalização associado tanto às altas temperaturas (com um atraso até 5 dias) como às baixas temperaturas (com um atraso de 5-15 dias), embora as associações fossem fracas. Um estudo anterior realizado em múltiplos cenários também sugeriu uma ligação com a temperatura, com taxas mais elevadas de infecção por VSR durante dias com temperaturas entre 2°C-6°C em regiões temperadas e entre 24°C-30°C em regiões quentes e húmidas.³ Os residentes de Hong Kong parecem estar vulneráveis

em ambos os extremos da distribuição da temperatura, observando-se também uma distribuição sazonal bimodal para a gripe na cidade, como também noutras regiões entre os trópicos e subtropicais.⁴ Se as distinções na sazonalidade da bronquiolite e os efeitos da temperatura nas regiões temperadas em comparação com outras partes do globo partilham características semelhantes às da gripe, justifica-se a realização de mais estudos centrados na bronquiolite em regiões tropicais e subtropicais.

O presente estudo também observou efeitos adversos consistentes em todos os poluentes considerados, à exceção do ozono.² Apesar das evidências substanciais dos efeitos nocivos do ozono sobre a saúde respiratória, Leung *et al* sugerem que a associação não positiva encontrada pode estar relacionada com a atividade virucida do ozono e o seu efeito sobre as defesas do hospedeiro. Embora tenha sido relatado que o ozono é um agente eficaz na inativação do vírus transmitido pelo ar num estudo realizado numa câmara de ensaios laboratoriais,⁵ não é provável que este seja o caso em Hong Kong, uma vez que a dose necessária para inativar o vírus é muito mais elevada do que os níveis de ozono ambiental presentes na cidade. Estudos em ratos sugerem que a exposição ao ozono promove respostas imunitárias contra infecções virais através da indução de interleucina-3 e do aumento da resposta antiviral dos linfócitos T CD8+.⁶ Os mecanismos e os efeitos reais dos potenciais efeitos nocivos e potencialmente benéficos do ozono sobre a saúde respiratória humana continuam por esclarecer e merecem uma investigação mais aprofundada. Isto pode ser particularmente oportuno e crítico na atual pandemia global da COVID-19. Além disso, o ozono ambiental está positivamente correlacionado com o nível de radiação ultravioleta e a radiação ultravioleta B (UVB) está negativamente associada à atividade epidémica do VSR.³ Infelizmente, a radiação UVB não foi incluída no estudo de Hong Kong. Por conseguinte, não podemos descartar o efeito confundidor da radiação UVB na associação negativa aguda observada com o ozono. Relativamente a outros poluentes, o estudo de Leung *et al* sugere que a poluição atmosférica tem maiores impactos agudos comparativamente aos fatores climáticos nas hospitalizações por bronquiolite entre crianças mais novas.² Os níveis médios diários de dióxido de azoto (NO₂) apresentaram um limiar em torno do nível mediano de 50 µg/m³.

Este valor é difícil de comparar com os limites estabelecidos na diretriz de qualidade do ar da OMS para NO₂, uma vez que a mesma se baseia em medições diferentes - não excedendo uma média de 200 µg/m³ por hora e uma média anual de 40 µg/m³. Porém, as partículas em suspensão (PM₁₀) demonstraram impactos adversos pelo menos a partir do percentil 25 de 24 µg/m³ em intervalos

de 0-2 dias. Como a diretriz da OMS para a média de PM₁₀ por 24 horas é de 50 µg/m³, isto pode não ser suficientemente restritivo para proteger a saúde respiratória das crianças. Em 2013, o governo de Hong Kong introduziu um sistema de alerta sobre o Índice da Qualidade do Ar (AQHI: *Air Quality Health Index*) para proteger a saúde pública dos efeitos nocivos da poluição atmosférica. O AQHI é baseado na média móvel de 3 horas de poluentes atmosféricos prioritários na cidade e é acompanhado por conselhos de saúde para grupos vulneráveis. A eficácia do AQHI na redução de internamentos hospitalares por infecções respiratórias foi previamente demonstrada, particularmente entre as crianças (<18 anos de idade).⁷

Outras estratégias podem ajudar a reduzir o fardo da bronquiolite entre as crianças muito jovens. Em Hong Kong, os escapes de veículos a gás são uma das principais fontes de matéria particulada. Assim, estratégias ambiciosas para reduzir ainda mais a matéria particulada, tais como a mudança completa para veículos de zero emissões, conforme estipulado pelo governo do Reino Unido até 2050, irão provavelmente proporcionar grandes benefícios para a saúde respiratória em geral. Embora louváveis, esses objetivos não abordam a predominância de automóveis em ambientes urbanos. Uma mudança para uma cidade mais propícia a deslocamentos a pé em detrimento dos automóveis - um modelo que já está a ser defendido em Hong Kong⁸ - ajudaria a proporcionar ainda maiores benefícios para a saúde e o meio ambiente.

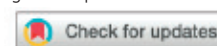
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ARTIGO ORIGINAL INVESTIGAÇÃO

Associação a curto prazo entre variação meteorológica, poluição do ar exterior e bronquiolite aguda em crianças em ambiente subtropical

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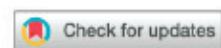
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RESUMO

Objetivos Examinar a associação entre a hospitalização de crianças relacionada com bronquiolite aguda, variação meteorológica e poluição do ar exterior.

Métodos Obtivemos os registos diários de admissão de bronquiolite aguda de crianças ≤ 2 anos de idade em todos os hospitais públicos, os dados meteorológicos e as concentrações de poluentes atmosféricos no exterior entre 1 de janeiro de 2008 e 31 de dezembro de 2017 em Hong Kong. Utilizamos modelos aditivos generalizados de quasi-Poisson juntamente com modelos não lineares (*distributed lag*) para estimar as associações de interesse ajustadas para confundidores.

Resultados Foi incluído na análise um total de 29 688 admissões. O aumento do risco relativo ajustado (RRa) de hospitalização relacionada com bronquiolite aguda foi associado à temperatura elevada (temperatura ambiente e temperatura aparente) e foi marginalmente associado à elevada pressão de vapor, um substituto para a humidade absoluta. A elevada concentração de NO₂ foi associada a um risco elevado de admissão por bronquiolite aguda. O risco de hospitalização por bronquiolite aumentou estatisticamente de forma significativa com a exposição cumulativa de NO₂ na gama 66,2–119,6 µg/m³. Relativamente às PM₁₀, o efeito significativo observado em concentrações elevadas parece ser imediato, mas não duradouro. Relativamente ao SO₂, a RRa aumentou à medida que a concentração se aproximou do percentil 75 e, depois, diminuiu, embora a associação fosse insignificante.

Conclusões A hospitalização aguda por bronquiolite entre crianças foi associada à temperatura e exposição a NO₂ e PM₁₀ em diferentes *lag times*, sugerindo a necessidade de adoção de políticas sustentáveis de ar limpo, especialmente para atuar sobre os poluentes produzidos pelos veículos motorizados, de modo a proteger a saúde das crianças jovens.

INTRODUCTION

Acute bronchiolitis is typically caused by viral infection. Respiratory syncytial virus (RSV) is the most common pathogen in childhood respiratory tract infection, especially among those ≤ 2 years old.^{1–3} Clinical signs and symptoms of acute bronchiolitis include cough, tachypnoea, hyperinflation of lungs, chest retraction, inspiratory crackles and expiratory wheeze.^{2,3}

Acute bronchiolitis causes significant morbidity and mortality among infants and young children worldwide.¹ It is the most common cause of lower respiratory tract infection (LTRI)-related

Key messages

What is the key question?

► Are meteorological variation and outdoor air pollution associated with acute bronchiolitis-related hospitalisation in children?

What is the bottom line?

► Acute bronchiolitis-related hospitalisation among children was associated with temperature and exposure to NO₂ and PM₁₀ at different lag times.

Why read on?

► This is one of the very few studies that explored the association of interest in a subtropical setting.

hospitalisation.^{1–3} In the USA, acute bronchiolitis is the leading cause of hospitalisation among infants ≤ 1 year old.⁴ Nearly all children would be infected at least once by the time they reached the age of 2 years, and an estimated 2%–3% of all children would be hospitalised with acute bronchiolitis during their first year of life.^{2,3,5,6} In temperate regions, the annual epidemics usually last from November all the way till April with a peak observed in January or February.^{5,6} Similar patterns could be seen in European countries where the average RSV season commences in the beginning of December, peaks in early February and ends in early April.⁷

In Hong Kong, acute bronchiolitis is one of the major causes of hospital admissions among infants under the age of one. Up to 5% of total paediatric discharge from all hospitals under the Hong Kong Hospital Authority are attributed to this condition.⁸

In a single hospital study, the estimated incidence of bronchiolitis hospitalisation was 21 per 1000 among children ≤ 2 years old with 86% of them having been infected with RSV.⁹ Different from the USA and Europe, Hong Kong is located within the subtropical region where RSV season remains illdefined but usually overlaps with the rainy season (ie, from March to September).^{3,8}

Global surveillance suggested that the seasonal periodicity of RSV infection is related to climatic factors.¹⁰ Meteorological conditions including ambient temperature, rainfall and

humidity were reported to be associated with RSV activity,^{6–10–12} while altitude, wind speed, dew point and ultraviolet B radiance were reported to be associated with bronchiolitis.^{11–12} On the other hand, air pollutants such as primary traffic pollutants, ozone (O₃), fine suspended particulates (PM_{2.5}) and environmental nitrogen dioxide (NO₂), as well as living close to major roadways have been reported to be associated with exacerbation of respiratory infections in young children.^{13–14}

Hong Kong is a densely populated cosmopolitan city in southern China with hot and humid summers, and mild and dry winters. According to the 2016 Population By-census, Hong Kong had a population of 7.34 million.¹⁵ Motor vehicles are the main source of air pollutants in Hong Kong. According to the air quality guideline of the WHO, 8 hours daily mean of O₃ should not exceed 100 µg/m³, while annual mean level of respirable suspended particulates (PM₁₀) and NO₂ should not exceed 20 µg/m³ and 40 µg/m³, respectively.¹⁶ Unfortunately, in Hong Kong, the highest 8 hours mean concentration recorded for O₃ was 305 µg/m³ and the highest annual mean concentrations recorded for PM₁₀ and NO₂ were 46 µg/m³ and 97 µg/m³, respectively, in 2017, all of which exceeded the WHO's guideline limits.¹⁷

Previous studies suggested that acute bronchiolitis-related hospitalisation in children is associated with meteorological variation but its association with outdoor air pollution has not been well explored.^{6–9–14–18–19} Furthermore, only limited studies have been conducted in subtropical regions, most of which yielded inconsistent results.^{8–9–18–19} Therefore, in this study, we aim to evaluate the possible short-term association among acute bronchiolitis-related hospitalisation in children, meteorological variation and outdoor air pollution in Hong Kong.

METHODS

Study design

This is a retrospective time-series study to assess the short-term impacts of meteorological variation and outdoor air pollution on acute bronchiolitis-related hospitalisation among young children. We obtained the daily counts of acute bronchiolitis-related admission of children ≤2 years old from a total of 12 public hospitals with acute paediatric inpatient services, daily meteorological data and daily outdoor air pollutants' concentrations between 1 January 2008 and 31 December 2017.

Hospital admission data

In Hong Kong, paediatric care services are provided by both the public and private sectors. Approximately, 71% of all hospitalisations in 2016 occurred in public hospitals.²⁰ The retrospective data of admissions of children ≤2 years old to all public hospitals for acute bronchiolitis (International Classification of Diseases 9th version (ICD-9): 466.¹ in principal and secondary diagnosis) from 1 January 2008 to 31 December 2017 were extracted for statistical modelling. Data on influenza-associated hospital admission (ICD-9: 487.0, 487.1, 487.8) were also collected.

Meteorological data

Daily meteorological records measured at a single central monitoring station run by the Hong Kong Observatory were obtained for the study period, including mean ambient temperature (°C), mean relative humidity (RH%) and total rainfall (mm), from the open-access data available on their website (https://www.hko.gov.hk/cis/climat_e.htm). Actual vapour pressure (hPa), a proxy for absolute humidity well adopted in many environmental studies^{21–22} was then derived using Teten's formula²³:

$$e = \frac{RH}{100} \times 6.105 \times \exp\left(\frac{17.27 \times TEMP}{237.7 + TEMP}\right)$$

where *e*, RH and TEMP denote actual vapour pressure, relative humidity and ambient temperature, respectively. Apparent temperature (°C) was derived using the following formula²⁴:

$$\text{Apparent temperature} = 1.04 \times TEMP + 0.2 \times e - 0.65 \times WIND - 2.7$$

where TEMP and *e* are as defined above and WIND denotes wind speed (m/s).

Ambient air pollutants data

Daily average levels of air pollutants measured at 13 general air monitoring stations (Central/Western, Eastern, Kwai Chung, Kwun Tong, Sham Shui Po, Shatin, Tai Po, Tap Mun, Tseng Kwan O, Tsuen Wan, Tuen Mun, Tung Chung and Yuen Long), including nitrogen dioxide (NO₂), sulphur dioxide (SO₂), ozone (O₃) and particulate matters (PM₁₀), were retrieved from the official website of the Environmental Protection Department of Hong Kong (<https://cd.epic.epd.gov.hk/EPICDI/air/station/?lang=en>). Data from Tap Mun station were excluded because it is situated in a remote area with very low population density, thus, might not represent the exposure of the general population. Data from the remaining 12 general air monitoring stations were averaged for downstream analysis.

Statistical analyses

Descriptive statistics were used to describe the demographic characteristics of the patients. A quasi-Poisson generalised additive model was used in conjunction with the distributed lag non-linear models (DLNMs) to assess the potentially lagged non-linear short-term associations between acute bronchiolitis-related hospitalisation of young children, meteorological variation and outdoor air pollution. In the DLNM, cross-basis is a bidimensional functional space created by combining two pre-selected sets of basis functions, which specify the relationships in the dimensions of an independent variable and lags, respectively. Algebraically, the cross-basis function of an independent variable *X* at time *t* with a maximum lag of *L* can be expressed in the following form:

$$cb(X, t, L) = \sum_{j=1}^{v_x} \sum_{k=1}^{v_l} r_{tj}^T c_k \eta_{jk}$$

where *r_{tj}* is an (L + 1) × 1 vector representing the *j*th basis variable of *X* across the (L + 1) lags, *c_k* is an (L + 1) × 1 vector obtained by transforming the lag vector *l* = [0, 1, ..., L] using the *k*th basis function in the lag dimension, *v_x* and *v_l* are the dimensions of the basis functions of *x_t* and respectively, and *η_{jk}* is the unknown regression coefficient.²⁵

The form of the primary model is as follows:

$$\begin{aligned} \log[E(Y_t)] = & + cb(TEMP, t, L) + cb(RH, t, L) + \\ & cb(\text{factor}(RAINFALL), t, L) + \\ & cb(NO_2, t, L) + cb(\log(PM_{10}), t, L) + \\ & cb(O_3, t, L) + cb(\log(SO_2), t, L) + \\ & cb(\text{factor}(HOLIDAY), t, L) + ns(DOS, df = 7 \text{ per year}) + \\ & \text{factor}(DOW_t) + s(\sqrt{FLU_t}, k = 7) \end{aligned}$$

where *E(Y_t)* is the daily expected count of acute bronchiolitis admissions on day *t*; TEMP, RH, RAINFALL denote ambient temperature, relative humidity, and total rainfall, respectively; DOS_t and DOW_t denote day of study and day of week on day *t* respectively; α is the overall intercept; factor(.) is a set of indicator functions for any categorical independent variable, and *s*(.) denotes a smoothing spline function with maximum basis dimension *k*. In this study, natural cubic spline functions (ns) with 2 and 3 knots placed at equally spaced intervals were chosen as the basis function of the meteorological parameters

(except for rainfall) and pollutants, respectively, which is equivalent to 3 and 4 degrees of freedom (*df*) respectively; whereas an ns function with 2 knots placed at logarithmically equal intervals, which is equivalent to 4 *df*, was selected as the basis function of lag. DOS was modelled using an ns function with 7 *df* per year. The incubation period for acute bronchiolitis is usually 5–7 days and disease period is usually 1–2 weeks⁵; hence, the maximum lags for independent variables were assumed to be 21 days. Total rainfall was categorised into three groups, namely 0mm, 0 to 38.8mm (the 95th percentile) and >38.8mm, so as to better examine the effect of extreme rainfall and reduce the influence of outliers.²⁶ SO₂ and PM₁₀ were log transformed to reduce skewness and the influence of outliers. An indicator variable HOLIDAY which denotes whether a specific day was a holiday, DOS, DOW and the square root of the number of influenza-associated hospital admission on the same day (FLU) were included in the model for confounder control. To further assess the adjusted effect of absolute humidity and apparent temperature on the daily counts of acute bronchiolitis admissions, two secondary models with vapour pressure in place of ambient temperature and relative humidity, and apparent temperature in place of ambient temperature were fitted due to high correlations between these meteorological variables (online supplemental appendix section A).

All results were reported in terms of overall cumulative adjusted relative risks (ARR), which accumulated the ARR over the lag period of 21 days, along with the corresponding 95% CI, and ARR plots by lag at selected percentiles, at which the adjusted risks at a specific lag and percentile were compared with that at the reference value on the concurrent day. The reference values for rainfall and all pollutants were 0mm and their corresponding 5th percentile, respectively, whereas the medians were chosen as the reference values for ambient temperature, apparent temperature, relative humidity and vapour pressure.

Model diagnostics and sensitivity analysis

Adjusted R² and residual plots were used to assess the goodness of fit of the final models. Partial autocorrelation function (PACF) plots were used to assess partial autocorrelation of residuals, with absolute values of pacfs <0.1 at the first 30 lag days regarded as adequate fit.²⁷ Sensitivity analyses were conducted to assess the robustness of the final results to the initial model choices. To be specific, changes in the overall cumulative ARR induced by the alternation of the *dfs* of the basis functions for meteorological parameters (2 and 4 except for rainfall), pollutants (3 and 5), and lag dimensions (3 and 5), as well as that of ns function for DOS (6 and 8 per year) were examined. The cut-off values for categorising total rainfall were also altered (online supplemental appendix section B).

All statistical analyses were performed using R V.3.6.0. (R Development Core Team, 2018: <https://www.rproject.org/>) and the raw outputs were listed in online supplemental appendix section E.

RESULTS

A total of 31523 admissions from 2008 to 2017 were retrieved from the database, out of which 1835 were elective admission, and thus, were excluded in the analysis. Among the remaining 29688 admissions, 66% were infants ≤12 months, 4% were pre-term babies (<37 weeks), 68% were male and 99% were Asian. The median (IQR) length of stay was 3 days (2–4 days). 21.5% of cases were admitted more than once with acute bronchiolitis. During the study period, a total number of 10 deaths were recorded, corresponding to a mortality rate of 0.04% (table 1). The major causes of these deaths were respiratory failure and multiple organ failure. Each hospital applies different practices based on different priorities. Some hospitals might not examine nasopharyngeal aspirates (NPA) for pathogens since the results would not affect their medical management. From the availa-

ble NPA results, RSV was the most common pathogen causing acute bronchiolitis in infants.

During the study period, the median (IQR) number of daily acute bronchiolitis admission was 8 (5–10) (table 2). The median (IQR) mean daily ambient temperature and mean relative humidity were 24.8°C (19.2°C–28.2°C) and 79% (74%–86%), respectively. According to the results, acute bronchiolitis was shown to exhibit seasonal pattern, with a major peak in spring (February–April) which could attain >400 cases per month, and a minor peak in late summer (September–October) having around 250 cases per month (figure 1).

Figure 2A–D show the overall cumulative ARRs and percentile specific (5th, 25th, 75th and 95th percentiles) ARRs of acute bronchiolitis-related hospitalisation among children ≤2 years old. The patterns of the overall cumulative ARR for ambient temperature and apparent temperature were similar, which showed an overall increasing trend (figure 2A,B). For ambient temperature, when the median (24.8°C) was taken as reference, the overall cumulative ARRs at the 5th, 25th, 75th and 95th percentiles were 0.990 (95% CI 0.721 to 1.361), 1.048 (95% CI 0.846 to 1.298), 1.034 (95% CI 0.904 to 1.182), and 1.108 (95% CI 0.871 to 1.409), respectively; whereas for apparent temperature, when the median (23.6°C) was taken as reference, resulted ARRs at the four percentiles were 1.005 (95% CI 0.761 to 1.326), 1.044 (95% CI 0.873 to 1.247), 1.112 (95% CI 0.962 to 1.286), and 1.323 (95% CI 1.011 to 1.731), respectively. It was found that, at the 75th and 95th percentiles of both ambient temperature and apparent temperature, the ARRs were statistically significant since lag 16–17 days.

For relative humidity (figure 2C), the overall cumulative ARR was comparatively higher when relative humidity was low compared with when it was high. When the median relative humidity (79.0%) was taken as reference, the overall cumulative ARRs at the 5th, 25th, 75th and 95th percentiles were 1.012 (95% CI 0.828 to 1.236), 0.987 (95% CI 0.901 to 1.080), 1.034 (95% CI 0.936 to 1.143) and 1.087 (95% CI 0.836 to 1.414), respectively. A delayed effect of high relative humidity (95th percentile) on the admission was evident: the estimated ARR was <1 from the concurrent day up to lag 4 days and was >1 afterwards.

The adjusted association between vapour pressure and the risk of acute bronchiolitis-related hospitalisation looked like a combination of the association of ambient temperature and that of relative humidity (figure 2D). Although the association appeared to be flattened U-shape, the risks were relatively higher at the higher end. Using median (24.7 hPa) as the reference value, the overall cumulative ARRs at the 5th, 25th, 75th and 95th percentiles were 1.056 (95% CI 0.851 to 1.311), 1.019 (95% CI 0.884 to 1.173), 1.070 (95% CI 0.903 to 1.267) and 1.125 (95% CI 0.864 to 1.466), respectively. While at the 5th percentile, the risk was relatively lower from the concurrent day to lag 3 days and was relatively higher up to lag 17 days. At moderately high (75th percentile) and very high (95th percentile) vapour pressures, the association was more complicated. The estimated ARR was >1 from lag 1 to 5 or 6 days as well as lag 15 days onwards, and was statistically significant since lag 18 days.

Total rainfall did not show a statistically significant relationship with the risk of hospitalisation adjusted for other variables in the model (figure 3). Nevertheless, there was apparently a harvesting effect at extreme rainfall (>38.8mm), at which the risk was relatively higher during the first few lag days. We have tested the robustness of different cut-off values for categorising total rainfall and our results were not sensitive to the variation (online supplemental appendix section B).

The overall cumulative effects and percentile-specific (25th, 50th, 75th and 95th percentiles) effects of the air pollutants on acute bronchiolitis-related hospitalisation among children ≤2 years old are shown in figure 4A–D. High concentrations of NO₂ were associated with elevated risks of acute bronchiolitis admis-

Table 1 Characteristics of the 29 688 patient episodes

Variable	N (%)
Admission	29 688
Emergency	
Admission age, months	
Mean (SD)	10.6 (6.6)
0–6 months	10 247 (34.5%)
7–12 months	9224 (31.1%)
13–18 months	6116 (20.6%)
19–24 months	4101 (13.8%)
Gestation age	
Preterm (<37 weeks)	1145 (3.9%)
Full term (≥37 weeks)	28 543 (96.1%)
Gender	
Male	20 147 (67.9%)
Female	9541 (32.1%)
Race	
Asian	26 418 (89.0%)
Non-Asian	452 (1.5%)
Unknown	2818 (9.5%)
Principal diagnosis	
Acute bronchiolitis	27 009 (91.0%)
Pneumonia	837 (2.8%)
Acute respiratory disease	392 (1.3%)
Gastroenteritis	314 (1.1%)
Croup	281 (0.9%)
Influenza	199 (0.7%)
Febrile convulsions	130 (0.4%)
Others for example, infection disease	526 (1.8%)
Length of hospitalisation (days)	
Mean (SD)	3.7 (12.6)
1	4815 (16.2%)
2	8312 (28.0%)
3	6180 (20.8%)
4	3760 (12.7%)
5	2301 (7.8%)
6	1532 (5.2%)
7	942 (3.2%)
>7	1846 (6.2%)
Unplanned readmission*	6383 (21.5%)
Death episode	10/23 305 (0.04%)
Viral agents	
Respiratory syncytial virus	9695/22 011 (44.0%)
Parainfluenzae	636/9607 (6.6%)
Metapneumovirus	424/6098 (7.0%)
Adenovirus	403/21 276 (1.9%)
Influenza A	71/6937 (1.0%)
Influenza B	18/6901 (0.3%)

Unplanned readmission is defined as any unscheduled emergency admissions due to acute bronchiolitis.

sion. In particular, the overall cumulative risk of bronchiolitis hospitalisation increased significantly when NO_2 was between 66.2 and 119.6 $\mu\text{g}/\text{m}^3$. The overall cumulative ARR at the 25th, 50th, 75th and 95th percentiles were 1.013 (95% CI 0.849 to 1.208), 1.038 (95% CI 0.831 to 1.297), 1.237 (95% CI 0.961 to 1.592) and 1.643 (95% CI 1.155 to 2.338), respectively. At high concentration of NO_2 , the estimated risk was statistically significantly higher after a lag of 2 weeks.

At very high concentrations of PM_{10} , the estimated overall cumulative adjusted risks tended to be higher than that at their corresponding 5th percentile despite statistical insignificance. For PM_{10} , the overall cumulative ARRs at the 25th, 50th, 75th and 95th percentiles were 1.084 (95% CI 0.916 to 1.282), 0.962 (95% CI 0.730 to 1.267), 0.793 (95% CI 0.572 to 1.099) and 0.756 (95% CI 0.522 to 1.094), respectively, and its effect appears to be immediate but not long lasting: the risk on the concurrent day was significantly higher at all percentile levels than if the exposure level had been the fifth percentile. The ARRs on the concurrent day at the four percentiles were 1.046 (95% CI 1.009 to 1.083), 1.056 (95% CI 1.005 to 1.110), 1.063 (95% CI 1.001 to 1.128) and 1.072 (95% CI 1.000 to 1.150), respectively.

For O_3 , the overall cumulative ARRs at the 25th, 50th, 75th and 95th percentiles were 0.838 (95% CI 0.703 to 1.001), 0.934 (95% CI 0.751 to 1.162), 0.965 (95% CI 0.758 to 1.230) and 0.962 (95% CI 0.711 to 1.301), respectively, except for the 25th percentile the risk tended to be higher during lag 1–7 days and was lower afterwards.

For SO_2 , the estimated ARR was above 1 when $\log(\text{SO}_2)$ was between 1.65 and 3.35, which was equivalent to the interval 5.21–28.5 $\mu\text{g}/\text{m}^3$ in the original scale. The overall cumulative ARRs at the 25th, 50th, 75th and 95th percentiles were 1.083 (95% CI 0.916 to 1.279), 1.179 (95% CI 0.952 to 1.460), 1.234 (95% CI 0.955 to 1.596) and 1.065 (95% CI 0.740 to 1.534), respectively. The patterns of ARR by lag at the four selected percentiles were similar. The estimated ARR was greater than 1 across lag 1–15 days.

Concerning model diagnostics, the adjusted R^2 of the primary model was 47.4%, and that of the two secondary models with apparent temperature and vapour pressure were 48.0% and 47.2%, respectively. The absolute values of PACFs of the residuals for the first 30 lags were all <0.1. In the sensitivity analyses, reducing the annual number of df for calendar time from 7 to 6 had the largest effect on the results (online supplemental appendix section C and D).

DISCUSSION

To our knowledge, few studies have investigated the short-term effects of meteorological variables and outdoor air pollution on acute bronchiolitis admissions in subtropical settings. In this study, a total of 29688 emergency paediatric acute bronchiolitis admissions from all Hong Kong public hospitals over a 10-year period were analysed and studied whether they were associated with meteorological variables and outdoor air pollutants. Our results showed that increased acute bronchiolitis-related hospitalisation was associated with high temperature (ie, ambient temperature and apparent temperature), and was marginally associated with absolute humidity. Although the result is generally in line with the study from Mäkinen *et al*²⁸, which showed an increasing trend in the risk of LTRIs when temperature and absolute humidity increased, we acknowledge that an effect of high temperature on bronchiolitis has not been well established in the literature. An investigation conducted in Malta suggested that majority of bronchiolitis-related hospital admissions occurred in winter in subtropical region,²⁹ while another study conducted in China indicated that ambient temperature was negatively correlated with bronchiolitis-related hospitalisations among children.³⁰ Yet, by now, there has not been much consensus within the field on 'risky' temperature range for acute bronchiolitis. This was similar with another study on pneumonia in children aged <5 years old where the temperature effect was inconsistent.³¹ Apart from that, a large proportion of admissions for LRTI (many of which were attributed to RSV) was shown to be independently associated with absolute humidity in children in northern Spain.³² Nevertheless, only limited literatures have documented the association between absolute humidity and acute bronchiolitis-related or RSV-related admissions, especially when compared with other respiratory infections such as influenza.^{21 22}

Among the air pollutants, high level of NO_2 was associated with increased risk of acute bronchiolitis admission and the overall effect became statistically significant over the range 66.2–119.6 $\mu\text{g}/\text{m}^3$ when compared with value at the 5th percentile. NO_2 is a common outdoor air pollutant primarily produced by motor vehicles and power plants as a byproduct of hightemperature combustion. At ambient pressure and temperature, NO_2 exists in its gaseous state and is relatively insoluble in water. These properties allow deeper penetration of NO_2 into the respiratory tree (ie, the lower respiratory tracts) where it would react with water from mucosal lining of the bronchioles and form corrosive chemicals including nitric and nitrous acids.³³ The nitrous vapour could cause microlesions in the respiratory tract and increase suscepti-

Table 2 Multiple logistic regression model incorporating seropositivity at time of study as the dependent variable and age, sex, ethnicity, Index of Multiple Deprivation score and department in which participants worked at the time of the study as independent variables

Variable	Unadjusted OR	95% IC	P Value	Z	Unadjusted OR	95% IC	P Value	Z
Age	—	—	—	—	0.98	0.96 to 1.00	0.60	0.55
Sex (female)	1.54	0.94 to 2.56	0.09	1.72	1.49	0.81 to 2.83	1.79	0.07
Ethnicity (BAME)	1.58	1.01 to 2.49	0.05	1.97	1.92	1.14 to 3.23	1.26	0.01
Index of Multiple Deprivation score	—	—	—	—	0.99	0.74 to 1.32	2.46	0.95
Acute medicine	1.60	0.76 to 3.37	0.24	1.17	0.99	0.34 to 2.86	0.01	0.99
Emergency department	0.47	0.10 to 1.81	0.31	1.01	0.36	0.05 to 1.69	1.19	0.23
Estates	0.61	0.18 to 2.00	0.43	0.78	0.57	0.11 to 2.29	0.75	0.45
General internal medicine	1.45	0.89 to 2.32	0.13	1.52	0.93	0.42 to 2.12	0.17	0.86
General surgery	0.45	0.14 to 1.37	0.19	1.30	0.24	0.03 to 1.05	1.71	0.09
Facilities	0.71	0.29 to 1.63	0.41	0.81	0.52	0.15 to 1.60	1.10	0.45
Housekeeping	1.68	0.79 to 3.62	0.19	1.30	1.01	0.31 to 3.09	0.02	0.99
Intensive care	0.50	0.24 to 1.01	0.06	1.87	0.28	0.09 to 0.78	2.37	0.02
Obstetrics and gynaecology	1.34	0.63 to 2.71	0.44	0.78	0.85	0.30 to 2.39	0.30	0.77
Research and development	0.71	0.33 to 1.50	0.38	0.88	0.44	0.15 to 1.22	1.54	0.12

Unadjusted OR and adjusted OR following multiple logistic regression are presented. OR presented for individual hospital departments represents the odds of seropositivity for individuals working in that department compared with not working in that department. Statistically significant OR are in bold ($p < 0.05$)

The area under the receiver operating characteristic curve of this model was 0.675 (95% CI 0.619 to 0.732, $p < 0.0001$).

BAME, Black, Asian and minority ethnic.

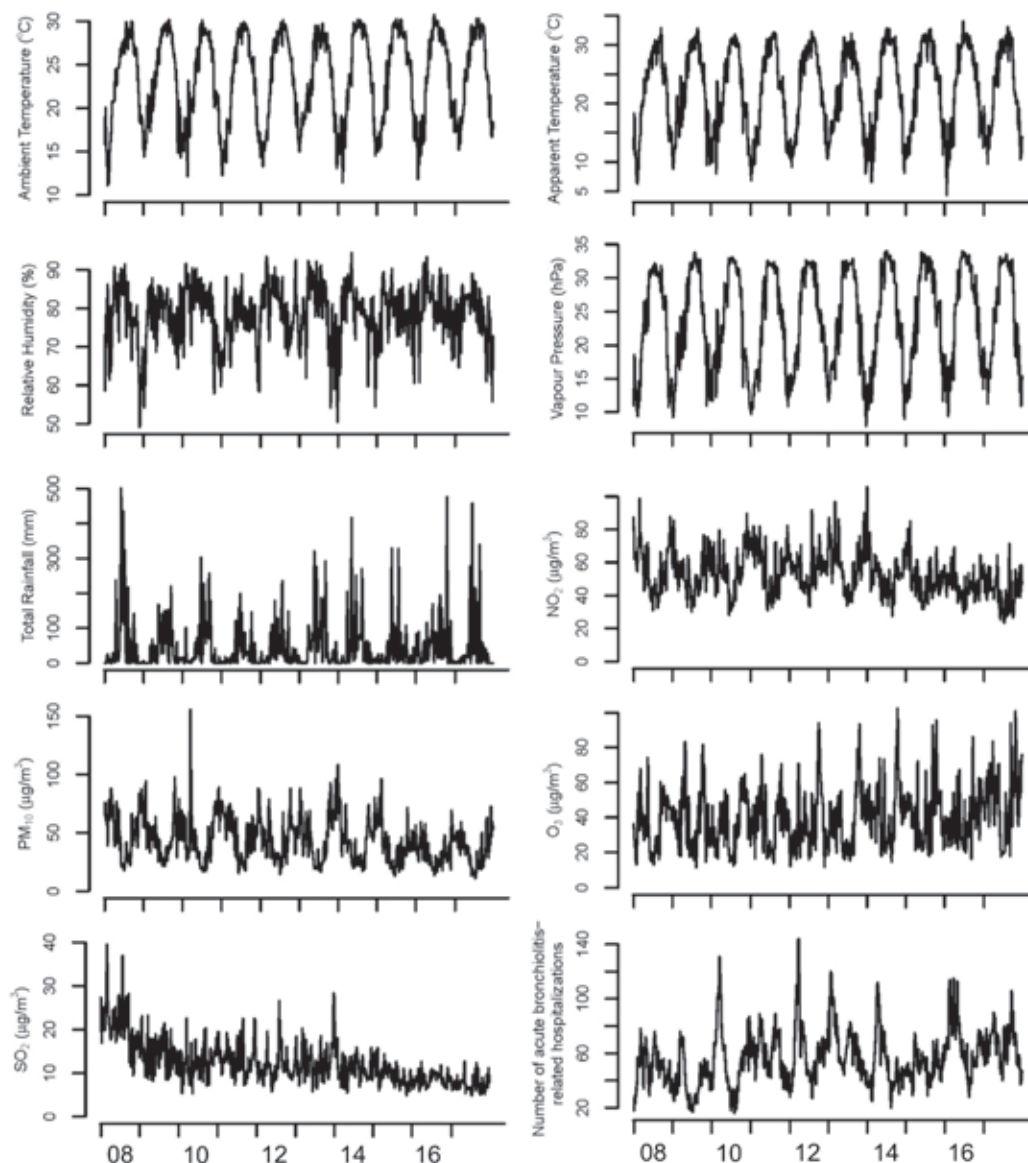


Figure 1 Seasonal variation in the weekly numbers of acute bronchiolitis-related admissions, meteorological parameters (monthly average ambient temperature, apparent temperature, relative humidity, vapour pressure and total rainfall), and air pollution level (monthly average nitrogen dioxide (NO_2), ozone (O_3), sulphur dioxide (SO_2), and PM_{10}) in Hong Kong during 2008 to 2017.

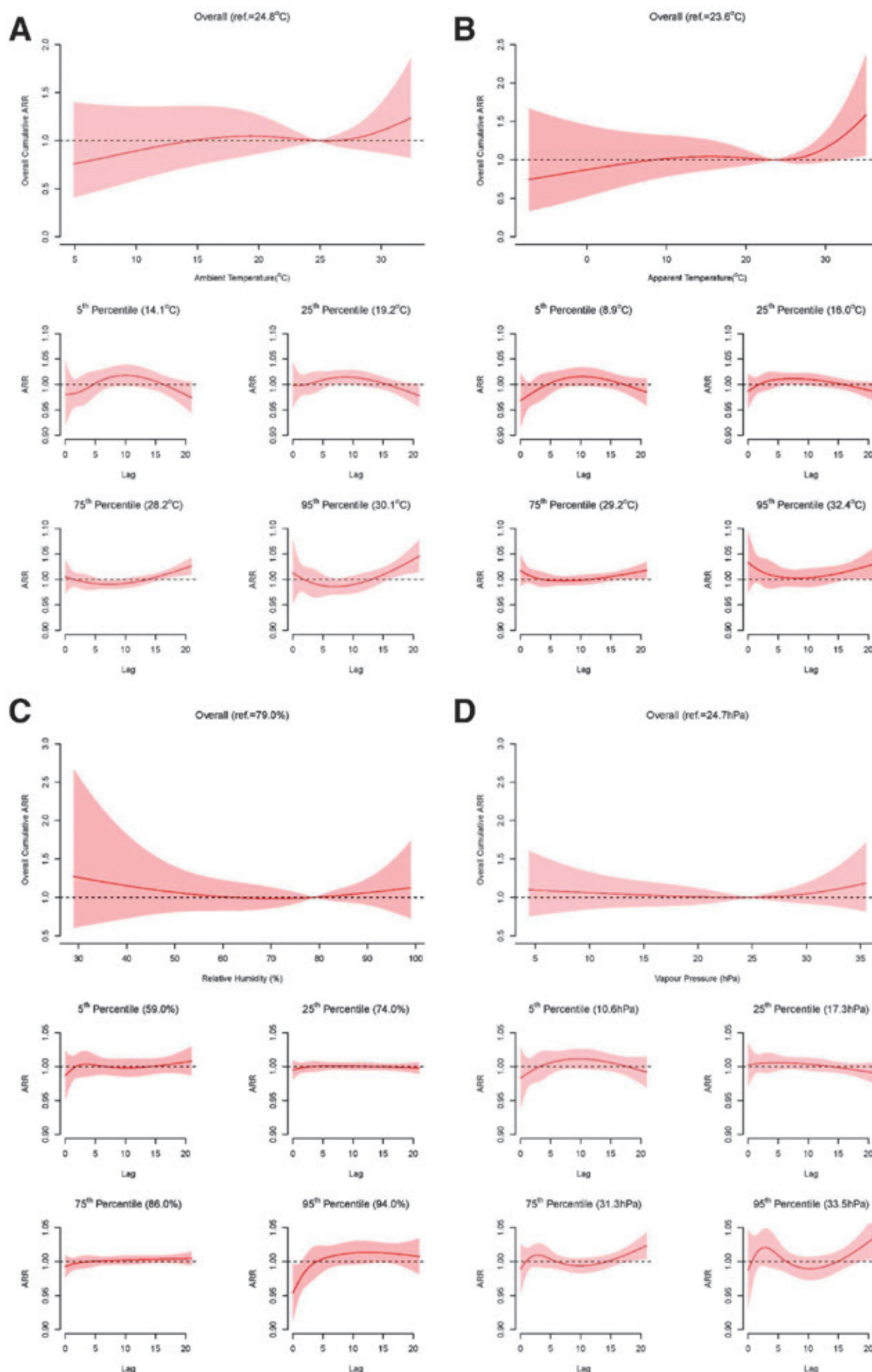


Figure 2 Overall cumulative adjusted relative risk along lags and adjusted relative risk by lag at selected percentiles against different meteorological variables. The reference values for (A) ambient temperature, (B) apparent temperature, (C) relative humidity and (D) vapour pressure for comparison were their corresponding median.

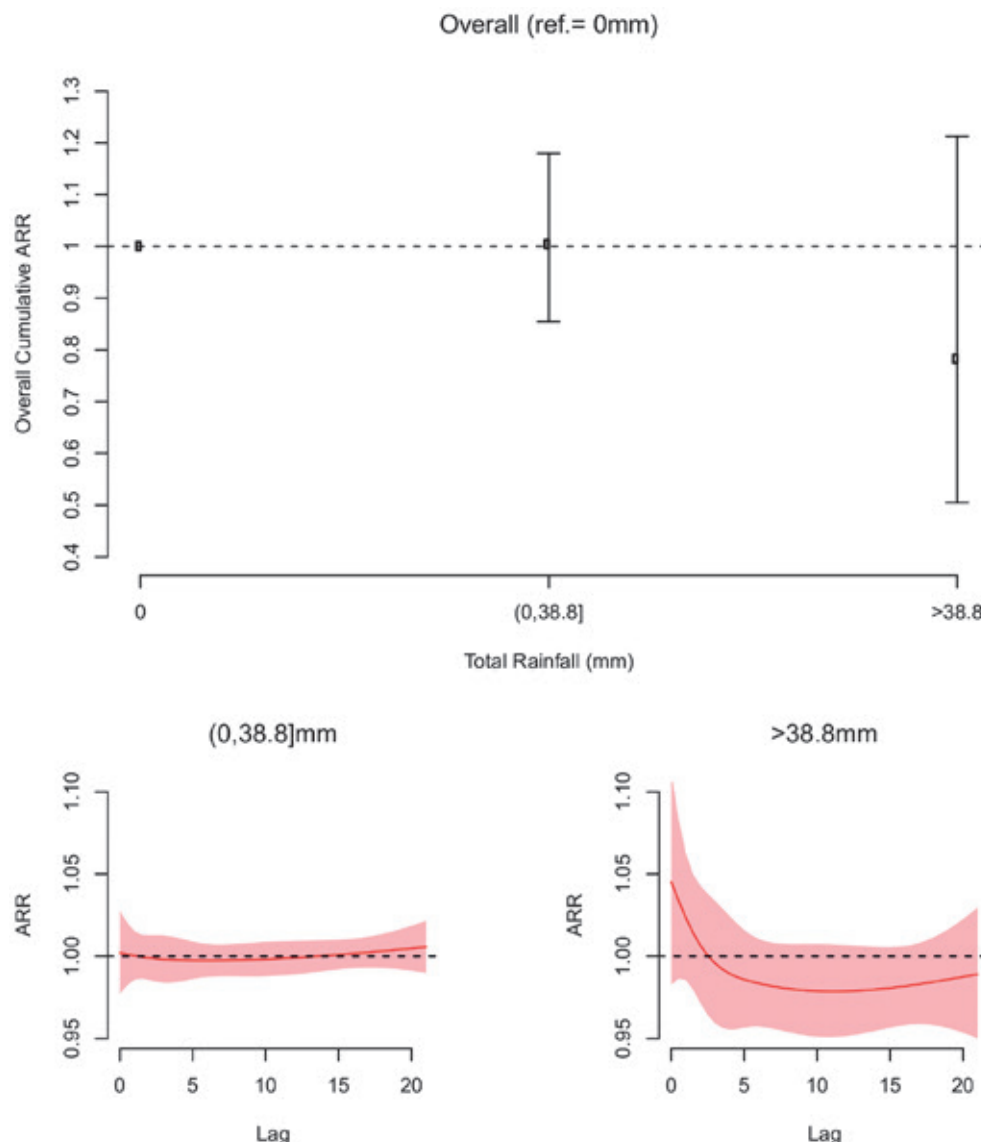


Figure 3 Adjusted cumulative relative risk along lags and adjusted relative risk by lag at selected percentiles against total rainfall. The reference value for a comparison was set to zero.

bility to infections, including those caused by RSV.³³ According to a recent large birth cohort study conducted in Indonesia among children aged 0–3 years, an IQR increase in NO_2 exposure would increase the risk for acute respiratory tract infection by an estimated 18%.³⁴ With reference to the WHO guideline for air quality, the annual mean level of NO_2 should not exceed $40 \mu\text{g}/\text{m}^3$.¹⁶ During our study period, the median (IQR) daily mean NO_2 level was $49.4 \mu\text{g}/\text{m}^3$ (39.6 to $62.5 \mu\text{g}/\text{m}^3$), and in 1770 days (48.5%) it exceeded the WHO's annual safe level.¹⁷ Considering the aforementioned, it is thus very important for Hong Kong to adopt sustainable clean air policies as soon as possible to protect young children's health. Regarding the sustained effect of NO_2 observed in our study, we tend to interpret the findings from toxicological perspectives. Seaton and Dennekamp³⁵ proposed the epidemiological association between illness and NO_2 might be confounded by particles number. Given the toxic effects of ultrafine particles has been evident at low concentrations in animals, we speculate the delayed effect of NO_2 might actually be the cumulative effect of successive exposure to ultrafine particles.³⁵ Follow-up studies should be conducted to test and verify this speculation.

A number of studies have been showing that exposure to PM would increase the risk of respiratory infections and other illnesses.^{13 36 37} In an investigation conducted in the USA, Karr et al¹³ found both chronic and subchronic exposures to $\text{PM}_{2.5}$ were associated with elevated risk of bronchiolitis hospitalisation in infants (ie, around a 9% increase in risk for every $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$). PM_{10} was found to be related to bronchiolitis consultation

and hospitalisation in both Malaysia and France.^{36 37} We found a significant positive effect of PM_{10} on acute bronchiolitis admissions only within a short time window, suggesting that most of the effects of PM_{10} were acute. This might explain why we did not find cumulative effects of PM_{10} over 21 days. One possible reason might be the relatively low PM_{10} concentration in Hong Kong (ie, $43.2 \mu\text{g}/\text{m}^3$) as compared with the WHO guideline level of $50 \mu\text{g}/\text{m}^3$ for 24hours mean. At low concentration, the adverse effect of PM_{10} on pulmonary health might not be clinically severe enough to cause hospitalisation, which might also explain why we could not find a cumulative effect of PM_{10} on bronchiolitis hospitalisations. Given that $\text{PM}_{2.5}$ has the ability to go even deeper into the lungs than PM_{10} does, and furthermore to enter the blood system, the damaging effect of $\text{PM}_{2.5}$ on respiratory health might be stronger than that of PM_{10} at low concentrations. It is thus speculated that replacing PM_{10} with $\text{PM}_{2.5}$ might be a better way to explore the overall cumulative risk of exposure to particular matters on acute bronchiolitis hospitalisation. Further research is needed to verify this hypothesis.

Similarly, no positive association was observed between O_3 and acute bronchiolitis admission. In a recent study, a 20-ppb increase in O_3 was associated with a significant increase in emergency department visits for respiratory conditions (by 1.7%–5.1%).³⁸ Children exposed to high ozone levels had significantly decreased lung function, which may have reduced their defence against viral infections (eg, RSV) and increased their susceptibility to bronchiolitis.³⁹ Nevertheless, it was argued that O_3 could

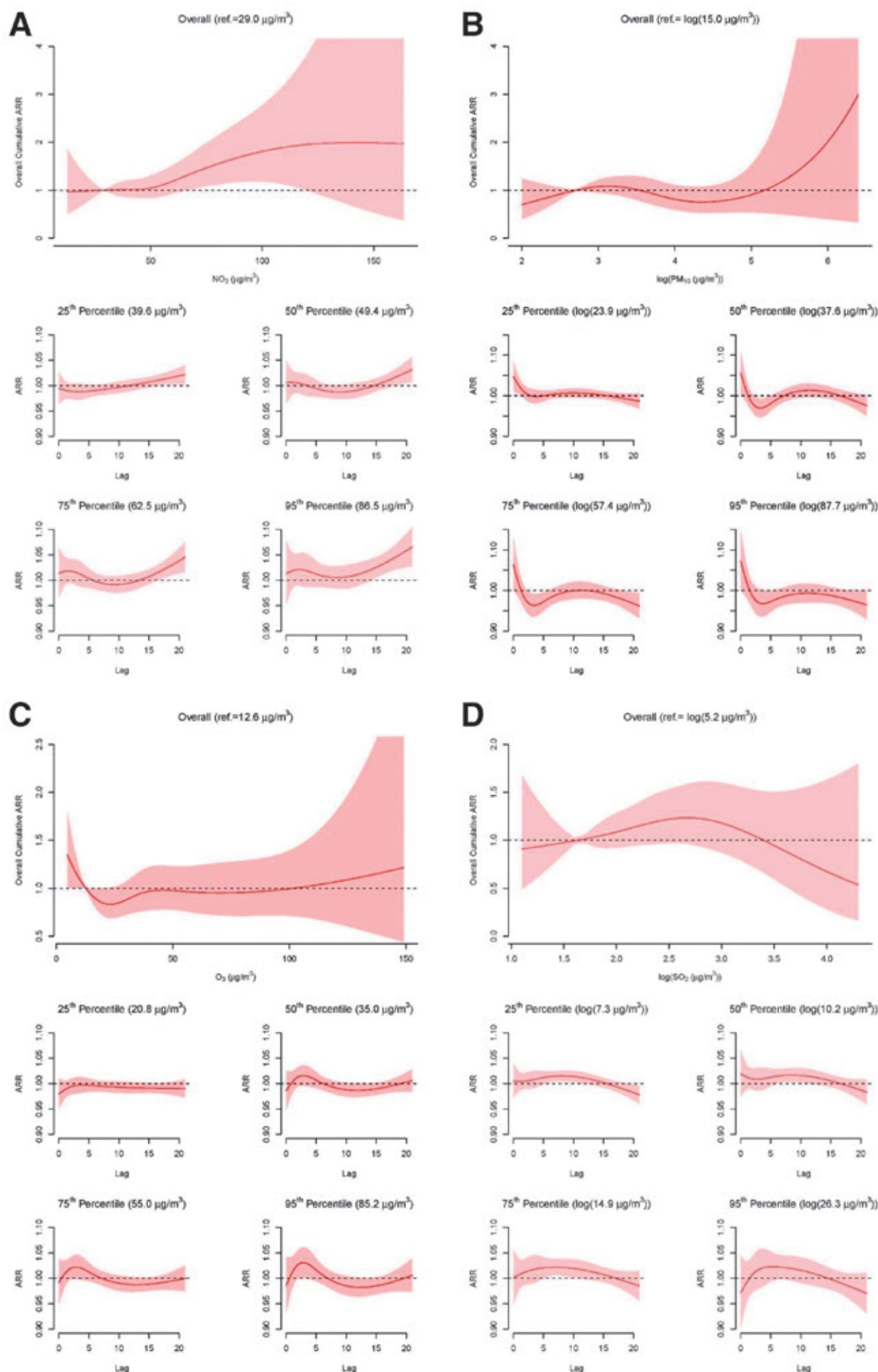


Figure 4 Overall cumulative adjusted relative risk along lags and adjusted relative risk by lag at selected percentiles against different pollutants, including (A) NO_2 , (B) PM_{10} , (C) O_3 , and (D) SO_2 . The reference values for comparison were their corresponding 5th percentile.

reduce the risk of respiratory infection that might be attributed to the virucidal activity of O_3 and its relationship with host defence.⁴⁰

The present study has several potential limitations. First, acute bronchiolitis is a clinical diagnosis, and therefore subject to variation among public hospitals due to differences in the availability of virus testing, differences in the diagnostic criteria used by doctors to diagnose bronchiolitis, and differences in coding practices. It is thus possible that acute bronchiolitis might be coded in the medical record system as other respiratory conditions. Meanwhile, criteria adopted in determining the need for hospitalisation changes over time. That being so, we might have underestimated the frequency of acute bronchiolitis hospitalisation in our study. Nevertheless, since over 90% of admissions in our dataset were principally diagnosed with acute bronchiolitis, our results shall remain robust (table 1). Second, this study used surveillance data in public hospitals which does not include data from private hospitals. However, the public healthcare services accounted for over 90% inpatient services in Hong Kong. Third, exposure measurement error is a common concern in environmental epidemiology, especially when studying the short-term impacts of environmental variables, given that meteorological condition and air pollutant levels change across time and space. For example, a child might be exposed to more air pollutants if she/he has smoking parents and lives in a household with 24 hours air conditioning that located close to busy roads. The error in exposure measurement might lead to inaccurate estimation of relative risks which, unfortunately, can hardly be avoided. Fourth, the increased incidence rate observed in this study might be affected by residual confounding. Unmeasured factors, such as parental smoking status, household crowding, indoor metrological condition (eg, temperature, relative humidity and air movement) and indoor air pollution (eg, NO_2 , PM_{10} , $PM_{2.5}$, O_3 , formaldehyde, volatile organic compounds, radon and airborne bacteria level) could be potential confounders and/or effect modifiers that might distort the results of the study. Fifth, given that different pathogens prefer different environment for survival and transmission,²¹ the findings of our study may not be consistent with results from pathogen-specific (eg, RSV, influenza, etc) analyses of acute bronchiolitis. We acknowledge the lack of information about pathogen causing the admissions is one of the main limitations in this study. Also, as RSV infection is a major determinant for acute bronchiolitis hospitalisation in children, we took the incubation period into account in addition to the symptomatic period and assumed a maximum lag of 21 days for the delayed effects in our study. Our results may thus be less compatible with other similar investigations that generally studied the short-term effects of pollutants using a shorter maximum lag (eg, 3–7 days). Last but not least, interaction effects between the meteorological factors and pollutants were not considered in this study. Our preliminary analysis has shown that although the interaction effects were not strong in general, when meteorological factors were at medium level and pollutants were at medium or high level, their joint effects on the outcome were usually statistically significant (detailed results not given), hence worth further investigation in future studies.

In conclusion, our findings showed that high temperature (ambient temperature and apparent temperature) and exposure to NO_2 and PM_{10} were associated with acute bronchiolitis-related hospitalisation among children at different lag times. The significant relationship with pollutants suggests the need to adopt sustainable clean air policies in Hong Kong, especially to target pollutants produced by motor vehicles, to protect young children's health. Since acute bronchiolitis continues to be a public health burden on the already-stressed healthcare system, policy-makers are urged to develop more cost-effective approaches to manage acute bronchiolitis in children. We believe that our findings

could rationalise an evidence-based allocation of resources and formulation of environmental policies to minimise the burden of disease associated with acute bronchiolitis in young children.

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Contributors SYL and KCC conceived the study. SYL, KCC and SYFL performed the analysis. KLK and SYL contributed to the acquired data of the study. SYL, PKSC, KCC and KM contributed to the results interpretation. SYL, KCC, SYFL, PKSC and KM drafted the paper. All authors have read and approved the final paper.

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Data availability statement Data may be obtained from a third party and are not publicly available. The sharing of data is restricted by the Hong Kong Hospital Authority.

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INSPIRA ESTABILIDADE¹ EXPIRA CONFIANÇA²



MAIOR ESTABILIDADE
NUMA ÚNICA TOMA.^{1,3}

O primeiro fôlego na DPOC.¹



LABA (LABA)



LAMA (LAMA)



LAMA (LAMA)

Laventair
umeclidínio + vilanterol ELLIPTA
ELE PROTEGE

Um perfil de segurança comparável ao tiotrópio e ao tiotrópio/olodaterol.⁴⁻⁶

1) Maltais *et al.* Respir Res. 2019;20(1):238. Laventair demonstrou menor probabilidade de ocorrência de CID vs. salmeterol e umeclidínio. A CID é considerada um marcador da estabilidade da doença, e foi um *endpoint* secundário do estudo. 2) Van der Palen J *et al.* NPJ Prim Care Respir Med 2016 26:16079. Em doentes com DPOC, o inalador Ellipta mostrou menor ocorrência de erros críticos em relação a todos os outros inaladores avaliados. 3) RCM Laventair Ellipta, fevereiro 2021. 4) Feldman GJ *et al.* Adv Ther. 2017;34:2518-2533. 5) Maleki-Yazdi MR *et al.* Respir Med. 2014;108:1752-60. 6) Decramer M *et al.* Lancet Respir Med. 2014;2:472-86.

CID: deterioração clinicamente importante; DPOC: doença pulmonar obstrutiva crónica; LABA: Agonista β_2 de longa duração de ação; LAMA: Antagonista muscarínico de longa duração de ação.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM

▼ 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 para <http://www.infarmed.pt/web/infarmed/submissao> e para o departamento médico da GlaxoSmithKline para lis.nucleo-farmacovigilancia@gsk.com.

NOME DO MEDICAMENTO LAVENTAIR ELLIPTA **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 65 microgramas de brometo de umeclidínio equivalente a 55 microgramas de umeclidínio e 22 microgramas de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 74,2 microgramas de brometo de umeclidínio equivalente a 62,5 microgramas de umeclidínio e 25 microgramas de vilanterol (como trifrenatato). **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose. **INDICAÇÕES TERAPÉUTICAS** Indicado como tratamento broncodilatador de manutenção para aliviar os sintomas em doentes adultos com doença pulmonar obstrutiva crónica (DPOC). **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Adultos A dose recomendada é uma inalação 1x/dia. Deve ser administrado à mesma hora do dia todos os dias para manter a broncodilatação. A dose máxima é uma inalação 1x/dia. Doentes idosos, Compromisso renal e Compromisso hepático ligeiro a moderado Não é necessário ajustar a dose. Utilizar com precaução em doentes com compromisso hepático grave. População pediátrica Não existe utilização relevante na população pediátrica (<de 18 anos) para a indicação de DPOC. Modo de administração Via inalatória. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** A reação adversa mais frequentemente notificada foi nasofaringite. **Infeções e infestações** Frequentes Infecção do trato urinário, sinusite, nasofaringite, faringite, infecção do trato respiratório superior **Doenças do sistema imunitário** Pouco frequentes Erupção cutânea Raros Anafilaxia, angioedema e urticária **Doenças do sistema nervoso** Frequentes Cefaleia Pouco frequentes Tremor, disgeusia Desconhecido Tonturas **Afeções oculares** Raros Visão turva, Glaucoma, Pressão intraocular aumentada **Doenças cardíacas** Pouco frequentes Fibrilhação auricular, taquicardia supraventricular, ritmo idioventricular, taquicardia, extra-sístoles supraventriculares, palpitações **Doenças respiratórias, torácicas e do mediastino** Frequentes Tosse, dor orofaríngea Pouco frequentes Disfonia Raros Broncospasmo paradoxal **Doenças gastrointestinais** Frequentes Obstipação, boca seca **Afeções dos tecidos cutâneos e subcutâneos** Pouco frequentes Erupção cutânea **Doenças renais e urinárias** Raros Retenção urinária, disúria, obstrução da saída da bexiga **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** fevereiro 2021. **APRESENTAÇÃO:** Laventair Ellipta 55 mcg+22 mcg, Pó para inalação 30 doses. **Regime de comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. **Medicamento Sujeito a Receita Médica.** Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM. Bial - Portela & C^ª, S.A., À Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. DMgMA_PT210311

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INNOVIVA



Bial
Keeping life
in mind.

Variabilidade de noite para noite de eventos respiratórios na apneia obstrutiva do sono: uma revisão sistemática e meta-análise

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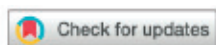
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RESUMO

Contexto É prática corrente utilizar-se um único estudo do sono para o diagnóstico da apneia obstrutiva do sono (AOS). No entanto, verificou-se uma variabilidade significativa de noite para noite (VSNN) de eventos respiratórios.

Métodos Avaliámos a VSNN de eventos respiratórios em adultos com suspeita de AOS ou AOS diagnosticada que foram submetidos a mais do que um estudo do sono. As fontes de dados foram as bases de dados PubMed, Cochrane e Embase, até 23 de janeiro de 2019. Foram utilizados modelos de efeitos aleatórios para a síntese das evidências. Para análise do moderador, realizou-se uma análise de regressão de efeitos mistos. O estudo foi registado com PROSPERO (CRD42019135277).

Resultados Dos 2143 artigos identificados, foram incluídos 24 estudos, compreendendo 3250 participantes. A diferença média do Índice de Apneia-Hipoapneia (IAH) entre a primeira e a segunda noite foi de -1,70/hora (95% IC -3,61 a 0,02). As diferenças de período REM (da primeira para a segunda noite) foram significativamente positivas e associadas a diferenças na média do IAH (coeficiente 0,262 (95% IC 0,096 a 0,428). Em média, 41% (95% IC 27% a 57%) de todos os participantes apresentaram alterações de eventos respiratórios >10/hora de uma noite para a outra. Adicionalmente, 49% (95% IC 32% a 65%) dos participantes mudaram a classe de gravidade da AOS (limiaries de gravidade de 5/hora, 15/hora e 30/hora) pelo menos uma vez em estudos de sono sequenciais. Dependendo do limiar de diagnóstico (5/hora, 10/hora ou 15/hora), em média 12% (95% IC 9% a 15%), 12% (95% IC 8% a 19%) e 10% (95% IC 8% a 13%) dos doentes, respetivamente, não teriam sido diagnosticados durante a primeira noite em caso de teste noturno único.

Conclusão Embora não se tenha verificado uma diferença significativa entre a média de IAH nas duas noites sequenciais de estudo a nível de grupo, verificou-se uma notável VSNN de eventos respiratórios entre os sujeitos conducente a diagnóstico e classificação erradas de doentes com suspeita de AOS.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common form of sleep-disordered breathing affecting up to 23.4% of middle-aged women and 49.7% of middle-aged men.¹ OSA is characterised by recurring episodes of partial or complete collapse of the upper airway during sleep, resulting in intermittent hypoxia, fragmented sleep, fluctuations in blood pressure and increased sympathetic nervous system activity.²

Current guidelines recommend to perform a single-night polysomnography (PSG) or home sleep apnoea testing (HSAT) in uncomplicated patients with clinically suspected OSA.³ The ApnoeaHypopnoea Index (AHI) provides the number of obstructive respiratory events of the upper airway per hour and is the main sleep study parameter used to diagnose or exclude OSA and to define disease severity. There is a considerable number of studies assessing night-to-night variability (NtNV) of respiratory parameters like AHI,⁴ Oxygen Desaturation Index (ODI)⁵ or Respiratory Disturbance Index (RDI).⁶ While some studies reported only mild NtNV of respiratory events,⁷ others suggested high variability raising the question whether a singlenight sleep study is inaccurate for diagnosis and treatment recommendations.⁵ There are conflicting

Key messages

What is the key question?

► Is there evidence for night-to-night variability of respiratory events in patients with obstructive sleep apnoea (OSA)?

What is the bottom line?

► Although there is no evidence for a relevant night-to-night variability of respiratory events on a group level, there is a remarkable intraindividual night-to-night variability among OSA patients affecting diagnostic accuracy and treatment decisions.

Why read on?

► This is the first comprehensive systematic review and meta-analysis summarising every available evidence about a topic of high clinical relevance in sleep medicine

data regarding intraindividual variability of respiratory parameters from night to night, which reported missed OSA diagnosis in 0%–55% of patients comparing one versus multiple sleep studies.^{8–10}

Undiagnosed and untreated OSA is associated with daytime sleepiness, decreased quality of life, increased risk for motor vehicle accidents, hypertension and possibly cardiovascular events - particularly stroke.^{2 11–15} In addition, the costs for diagnostic evaluation for OSA as well as for undiagnosed OSA are substantial,¹⁶ making a better understanding of NtNV of respiratory parameters imperative. There is also an increasing number of intervention studies in the field of OSA research which assess the effect of pharmacological or device-based interventions on respiratory parameters.¹⁷ The natural course of respiratory parameters from night to night should be considered in the design of interventional studies. However, solid evidence on NtNV is missing.

Several pathomechanisms and clinical predictors of increased NtNV of respiratory parameters have been discussed so far. Numerous studies demonstrated an association between the extent of NtNV of respiratory parameters and the severity of OSA.^{10,18–21} Sleep position and sleep stage could play an important role, since supine position and rapid eye movement (REM) sleep reduce the effectiveness of compensatory mechanisms to counteract upper airway collapse in OSA.²² While nasal congestion¹⁰ and states of increased body fluid²³ have been reported to rise NtNV, sex,²⁴ body mass index (BMI),²⁵ and age⁸ had no influence in previous studies.

We conducted a systematic review and meta-analysis to summarise all available evidence about NtNV of respiratory events in patients with suspected or diagnosed OSA. Our methods also allowed us to explore possible moderators that could have influenced this variability. To our knowledge, this is the first comprehensive review addressing this important topic in sleep medicine.

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METHODS

SEARCH STRATEGY AND SELECTION CRITERIA

We evaluated the NtNV of respiratory events in adults with suspected or already diagnosed OSA who underwent more than one diagnostic sleep study. The studies were identified through a search of PubMed, Cochrane and Embase by a medical data analyst specialised in systematic literature search. We also searched the ClinicalTrials.gov registry. The appendix provides all prespecified search terms used for each electronic database (online supplementary appendix table S1). We included articles in English, German and French. We also hand searched bibliographies of eligible papers to detect literature that might have been missed by the electronic database search (online supplementary appendix table S1). Two independent researchers separately assessed eligibility of the studies (MR and MB).

We included every prospective and retrospective study published before the 23 January 2019 that assessed NtNV of respiratory parameters in OSA if they: were original articles published in a journal; measured and reported variability of respiratory parameters (AHI, ODI or RDI) while off any OSA treatment; used an observational or interventional study design, the latter reporting NtNV of respiratory sleep parameters data of the control arm; provided data derived from PSG, respiratory polygraphy or a validated HSAT device (inclusive pulse oximetry); and provided data of at least two sleep studies. Studies were excluded if they: were case reports; included patients with only self-reported OSA; used non-validated devices to assess NtNV of respiratory sleep parameters; did not use the same diagnostic device within the same trial or reported time spans greater than 6 months between sleep studies. Only study reports on humans aged ≥ 18 years were considered eligible. We used only data reported in the articles and did not contact the authors for missing information because such data cannot be verified by the readers. In case of disagreement between the ratings of the independent researchers, consensus was reached by discussion or by a third researcher (MK).

DATA ANALYSIS

From every eligible study, two investigators (MR and MB) independently extracted all predefined data, using a standardised electronic spreadsheet according to the study protocol. Descriptive statistics were calculated on study level, that is, studies reporting on more than one study arm were entered only once. Publication year was given as range. All other continuous variables (eg, mean BMI or mean age) were reported with mean and SD. The number of patients was given

Table 1 Characteristics of the 24 included studies

No of included studies	24
No of analysed participants per study (median (IQR))	44.0 (21.5–85.8)
Female (% (SD))	29 (13.2)
Average age, years (mean (SD))	50 (13.2)
Average BMI, kg/m ² (mean (SD))	31.2 (3.1)
Average ESS, points (mean (SD))	11.8 (2.4)
Total sleep time first night, min (mean (SD))	358.2 (53.8)
Total sleep time second night, min (mean (SD))	379.6 (40.8)
Total sleep time diff. first to second, min (mean (SD))	-21.3 (22.8)
REM time first night, min (mean (SD))	71.8 (35.2)
REM time second night, min (mean (SD))	72.4 (22.2)
REM time diff. first to second, min (mean (SD))	-0.6 (18.5)
Prospective study design, n (%)	16 (66.7)
Multicentric, n (%)	6 (25%)
In-laboratory PSG, n (%)	15 (62.5)
At-home PSG, n (%)	2 (8.3)
In-laboratory respiratory polygraphy, n (%)	1 (4.2)
Home sleep apnoea testing, n (%)	5 (20.8)
Pulse oximetry, n (%)	1 (4.2)
>2 nights recording, n (%)	8 (33.3)
Average no of recording nights (mean (SD))	3.2 (2.6)
Maximum days between recording nights (mean (SD))	11.2 (2.4)
No of studies reporting on AHI, n (%)*	22 (91.7)
No of studies reporting on ODI, n (%)	1 (4.2)
No of studies reporting on RDI, n (%)	1 (4.2)

*One study reported AI instead of AHI.

AHI, Apnoea-Hypopnoea Index; BMI, body mass index; diff, difference; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; PSG, polysomnography; RDI, respiratory disturbance index; REM, rapid eye movement.

as median and IQR because patient numbers varied considerably between studies. Categorical variables on study level (eg, sex) were presented as numbers and percentages of total.

The outcome measures of this study included the assessment of NtNV of respiratory events reported on a group - or intraindividual level. The meta-analysis of the mean AHI difference between the first and second sleep study in the same participants was the main outcome of this study. A subgroup analysis analysed the differences in AHI values for in-hospital and home sleep studies. In those publications where mean and SD of AHI values were not reported, but instead median and IQR were reported, a formula proposed by Wan *et al*²⁶ was used for recalculation of mean and SD. If AHI values were reported in subgroups, the total mean and SD was calculated with weighted means.²⁶ AHI differences between two study nights other than between the first and the second study night were not analysed.

The intraindividual variability was addressed in the secondary outcomes as followed: we performed a meta-analysis of the proportion of patients having changed their OSA severity class, with severity thresholds of 5/hour, 15/hour and 30/hour. If more than two sleep studies were reported, we used the first night as reference to describe the following changes over multiple nights. The analysis was three-fold: (1) the proportion of patients with a general change in severity class in any direction was metaanalysed (treat the worst approach). Then, the proportion of patients changing into a (2) less severe OSA class or patients changing into a (3) more severe OSA class was meta-analysed. Furthermore, we meta-analysed the proportion of patients for whom an OSA diagnosis would have been missed in the first sleep study using three different AHI thresholds for OSA diagnosis (≥ 5 /hour, ≥ 10 /hour and ≥ 15 /hour). Additionally, we performed a meta-analysis on the reported proportion of patients with AHI changes higher than 10 between multiple sleep studies.

For the primary outcome assessment, mean differences between first and second night were meta-analysed assuming the correlation between repeated measurements to be 0.5 in the same patients across two nights. This assumption and its effect on the results was addressed in a sensitivity analysis, in which we let the correlation vary between 0.4 and 0.6. Furthermore, a sensitivity analysis was conducted, in which for the primary outcome, the summary estimate was obtained while excluding studies with high risk of bias.

For all binary outcomes, meta-analyses of proportions were calculated by dividing the number of patients with a certain condition by the total number of patients analysed. For pooling, logit transformed

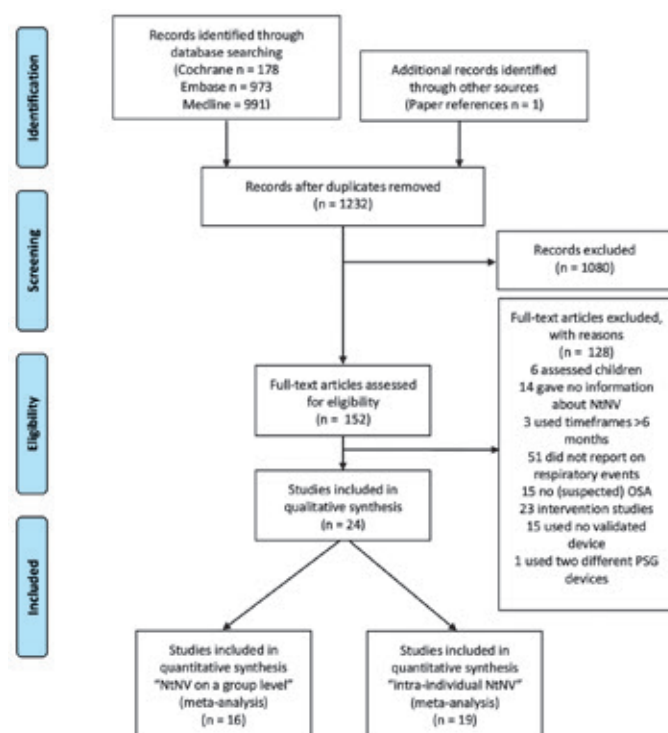


Figure 1 Flow diagram of the studies included in the review and meta-analysis. n, number of studies; NtNV, night-to-night variability; OSA, obstructive sleep apnoea; PSG, polysomnography.

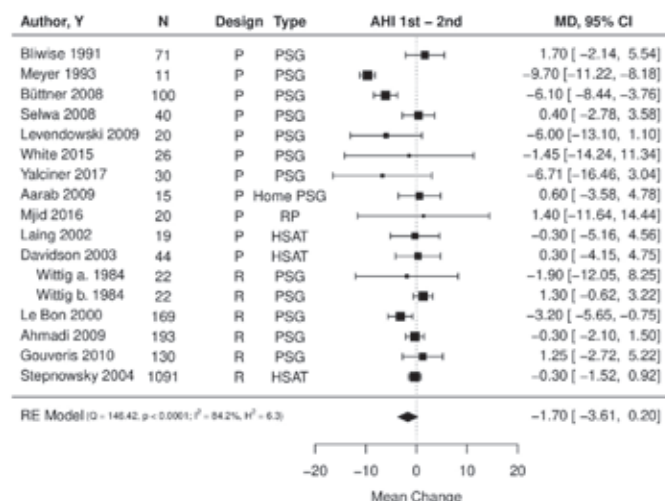


Figure 2 Forest plot of mean AHI change between the first and the second night. Kendall's $\tau = -0.265$, $p = 0.151$. AHI, Apnoea-Hypopnoea Index; HSAT, home sleep apnoea testing; n, number of analysed patients; PSG, polysomnography; p, prospective study design; Q, Cochran's Q test; R, retrospective study design; RE, random-effect; RP, respiratory polygraphy; Wittig a., part of the study by Wittig *et al.*⁴¹ referring to a subgroup of patients showing more than 100 apnoeas; Wittig b., part of the study by Wittig *et al.*⁴¹ referring to a subgroup of patients showing less than 100 apnoeas; Y, year.

proportions were used, with subsequent backtransformation to the original scale. Meta-analyses were carried out if at least three studies reporting on the same outcome could be identified. We used random effects models for all meta-analyses.²⁷

A prespecified list of moderators was evaluated one at a time regarding their effect on the estimated difference between the first and second sleep study with respect to AHI using mixed-effects meta-regression methods.²⁷ The list of moderators included the variables sleep study location, study design, difference in total sleep time from first to second night, difference in total REM time between first and second night, BMI, percentage of female sex, mean age and mean AHI in first night.

The test statistic and the p value of Cochran's Q test were reported for all meta-analyses, assessing whether residual heterogeneity was larger than would have been expected based on sampling variability alone. A $p < 0.05$ of the heterogeneity tests suggested that there was evidence for heterogeneous outcomes. In each of the meta-analyses, we calculated Cochran's Q test for heterogeneity with the corresponding p value, total heterogeneity over total variability (I^2), and total variability over sampling variability (H^2). Finally, to address funnel plot asymmetry, a rank correlation test was used, as proposed by Begg and Mazumdar.²⁸

All analyses were carried out with R (R Core Team (2019)), V.3.6.0, and meta-analyses were carried out with the R package metafor. Bias assessment was performed independently by two authors (TG and ST) using the National Institutes of Health's study assessment 'Quality of Observational Cohort and Cross-Sectional Studies'.²⁹ Disagreements in bias assessment between investigators were resolved by discussion and consensus. Reporting of the study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist³⁰ and MOOSE (meta-analysis of observational studies in epidemiology)³¹ guideline (online supplementary appendix table S10 and S11).

RESULTS

The systematic search identified 2142 manuscripts. After deduplication, two independent researchers (MR and MB) assessed 1232 studies for eligibility and ultimately included 24 studies,^{4–9 19 23 32–47} comprising 3250 participants (2446 analysed), for review and meta-analysis (figure 1). Subsequently, 16 and 19 studies underwent quantitative analysis regarding group mean changes and intra-individual variability of respiratory events from night to night, respectively. Demographic characteristics of included patients and methodological features of included studies are presented in table 1.

While 14 studies were prospective observational studies, eight followed a retrospective observational design and two were randomised controlled trials reporting only data from the control group. The number of participants analysed in the original study ranged from 15 to 1091 patients. On average, participants were mean (SD) 50 years (13.2) old and obese (mean (SD) BMI of 31.2 kg/m² (3.1)). They presented with increased subjective daytime sleepiness (mean (SD) ESS 11.8 (2.4)) and the majority were men. Further information about the study populations on study level are available in the appendix (online supplementary appendix table S3–S7). In 17 studies, PSG devices were used to assess NtNV and eight studies recorded more than two nights. All sleep study-related information—for example, used recording device, used scoring guidelines and time spans between sleep studies—are available in the online supplementary appendix table S8.

Sixteen studies reported data of mean AHI in two sleep studies.^{4 6 8 9 19 23 33 35 38 39 41–43 45–47} On average, AHI values were lower in the first night as compared with the second night with an estimated mean change of -1.70 /hour (95%CI -3.61 to 0.20) (figure 2). There was no evidence that this effect was different from zero. Heterogeneity was large in this meta-analysis, as indicated by a large I^2 value (84.2%) and also by a small p value in the Cochran's Q test ($p < 0.001$). The assumed correlation between the first and the second night in the same patients was 0.5 for this analysis. In a sensitivity analysis, the correlation was allowed to vary between 0.4 and 0.6, to assess whether the results would be robust to changes in the assumed correlation. The results were -1.73 /hour (95%CI -3.67 to 0.22) for an assumed correlation of 0.4 and -1.68 /hour (95%CI -3.54 to 0.18) for an assumed correlation of 0.6. Therefore, we conclude that the results can be considered robust. The risk of bias assessment resulted in three studies with high risk of bias. For the summary estimate of the primary outcome, two of these studies were originally included. The sensitivity analysis of the summary estimate without these two studies resulted in an estimate of -1.78 , with 95%CI -3.89 to 0.34 , indicating robustness of the results (online supplementary appendix figure S1).

The subgroup analysis between different sleep study locations (ie, in hospital vs at-home) revealed that mean AHI differences between two sleep studies were greater in the in-hospital setting (mean change -2.33 (95% CI -4.77 to 0.12)) than in the at-home setting where it was -0.20 (95% CI -1.19 to 0.79) (online supplementary appendix figure S2 and S3).

Of all moderators analysed, only for REM sleep differences (1st–2nd night), there was evidence for an association with mean AHI differences between two nights (β coefficient 0.262 (95% CI 0.096 to 0.428)). Even though the sleep study location in the hospital showed a clinically relevant negative association with mean AHI differences (β coefficient -2.386 (95% CI -6.671 to 1.900)), statistical significance was not reached. Since only a limited number of studies reported data on sleep position and total sleep time, these possible moderators were not included in moderator analysis. Table 2 lists the results of all evaluated moderators.

Table 2 Moderator analysis

Moderator	Beta coefficient	95%CI low	95%CI high	P Value	No of studies
Average age, years	0.012	-0.112	0.14	0.83	16
Female (yes/no)	-0.004	-0.146	0.137	0.952	15
Average BMI, kg/m ²	0.861	-0.095	1.817	0.078	12
AHI first night (/hour)	0.023	-0.143	0.188	0.79	17
Location: in-hospital (yes/no)	-2.386	6.671	1.9	0.275	17
Prospective study design (yes/no)	-2.289	6.048	1.471	0.233	17
Total sleep time diff. 1st–2nd (min)	0.022	-0.107	0.151	0.736	9
REM time diff. 1st–2nd (min)	0.262	0.096	0.428	0.002	7

Association between moderators and mean AHI 1st–2nd night.

AHI, Apnoea-Hypopnoea Index; BMI, body mass index; diff, difference; RDI, Respiratory Disturbance Index; REM, rapid eye movement.

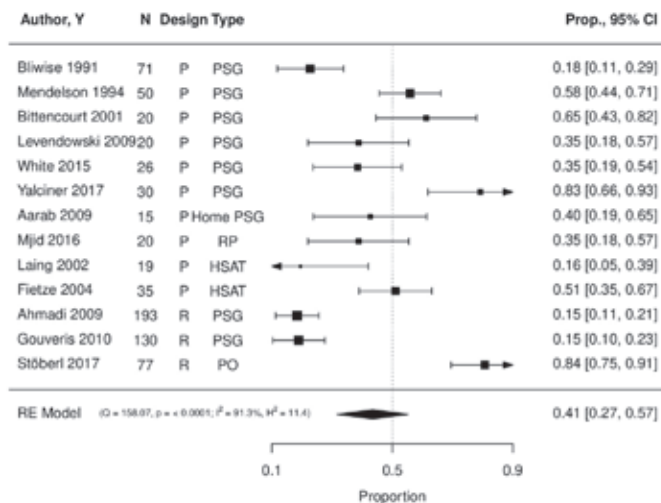


Figure 3 Forest plot of proportion of patients showing a change of respiratory parameters (AHI, ODI) of more than 10/hour in any direction among sequential measurement nights. Kendall's $\tau=0.224$, $p=0.296$. AHI, Apnoea-Hypopnoea Index; HSAT, home sleep apnoea testing n=number of analysed patients; ODI, oxygen desaturation index; PSG, polysomnography; p, prospective study design; Q, Cochran's Q test; R, retrospective study design; RE, random effect; RP, respiratory polygraphy; Y, year.

Nineteen studies reported on intraindividual NtNV of respiratory events in multiple study nights: 4–9 23 32–39 42 43 46 47. 13 studies reported an proportion of 41% (95% CI 27% to 57%) of patients presenting changes of respiratory events (AHI, ODI or RDI) greater than 10/hour from night to night (figure 3). Six studies reported the proportions of patients that changed OSA severity class (thresholds at 5/hour, 15 hours and 30/hour) during multiple nights of apnoea testing. On average, 49% (95% CI 32% to 65%) of the patients changed severity class at least once (online supplementary appendix figure S4). As presented in figure 4, studies using multiple sleep nights presented higher proportions of patients changing severity class. In addition, six studies provided data about the direction of severity class change—that is, towards an improvement or a worsening—in sequential nights (online supplementary appendix figure S5). While 15% (95% CI 12% to 20%) of participants changed into a less severe class, 18% (95% CI 13% to 26%) changed into a more severe OSA class after the first study night. There are several studies reporting on OSA diagnoses that would have been missed in the first sleep study using different thresholds (5/hour, 10/hour and 15/hour) (figure 5). Overall, across all thresholds the proportions were between 10% and 12%, roughly below 20% with their upper confidence limits. The studies showed larger heterogeneity for the thresholds of 5/hour and 10/hour when compared with a threshold 15/hour. We found no evidence for funnel plot asymmetry in any of the meta-analyses (all $p>0.05$).

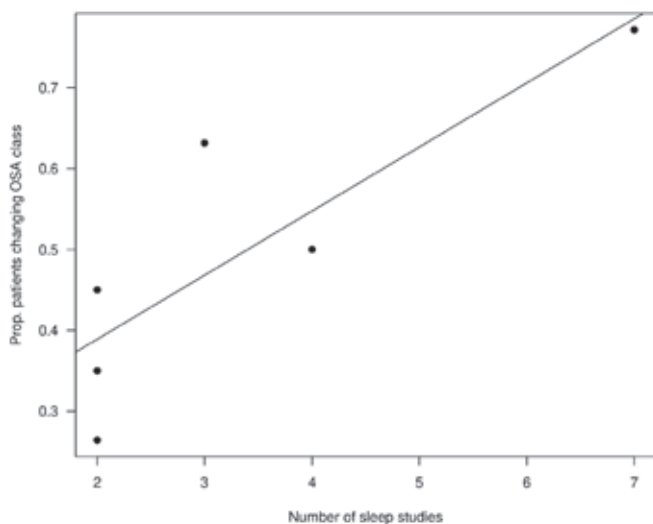


Figure 4 Scatter plot of six studies showing the proportion of patients changing OSA severity class in any direction as a function of the number of measurement nights. OSA, obstructive sleep apnoea.

The quality assessment revealed that most of the included studies were empirical and only one study reported an a priori sample size justification for the presented hypothesis. Outcome assessors were blinded in 29.2% of all studies. As expected, the scoring of the outcome was heterogeneous, as 38% of studies scored their sleep data according to the Rechtschaffen and Kales criteria, 28% according to the AASM guidelines and 34% according to other criteria. Only six studies considered the influence of medication and alcohol on NtNV. For further details, see online supplementary appendix table S9.

DISCUSSION

To the best of our knowledge, this is the first comprehensive systematic review to investigate NtNV of respiratory events in repeated sleep studies in patients with suspected or diagnosed OSA. While the NtNV of respiratory events reported on a group level was rather small, the meta-analysis revealed a remarkable intraindividual variability of respiratory parameters leading to high rates of missed OSA diagnosis and severity class changes from night to night. REM time differences might play an important role in the mechanism of the observed variability of respiratory events.

Our meta-analysis suggests that the number of respiratory events in two sequential sleep studies might not statistically differ on a group level. This might be attributable to a dilution of NtNV by the presence of both, patients who showed a lower AHI in the first night and patients who showed a higher AHI in the first night. We found the mean AHI to be higher in the second night, thereby contradicting those studies, which highlighted higher average respiratory event rates during the first night.^{4 35} Our results confirm the findings of the only other meta-analysis available regarding NtNV of respiratory parameters.³ The task force of the AASM guidelines performed a meta-analysis of only four observational studies assessing NtNV of AHI in two consecutive PSGs. They found the mean difference between two sleep studies to be 0.14 (95% CI –1.86 to 2.15) which was neither statistically nor clinically relevant. It is to mention that the AASM meta-analysis results are relevantly driven by a study that used at least two different PSG devices within the diagnostic process, which could have been a possible confounder. Although we included studies that used also nonconsecutive sleep study protocols and HSAT devices to measure respiratory parameters, the range of the confidence intervals between both meta-analyses were similar.

Our data suggested REM differences to be significantly associated with mean AHI differences in two sequential sleep studies. A majority of studies performing sequential, in-laboratory PSGs reported signs of classical 'first night effects',^{8 21 24 39 48} characterised by a reduction in REM sleep and total sleep time, reduced sleep efficacy, increased wake time after sleep onset and longer REM latency in the first night.⁴⁹ These sleep architecture

changes are assumed to be interconnected to the subjects' habituation process to the laboratory conditions.⁵⁰ Thus, the increased mean AHI difference in in-hospital sleep studies, observed in our meta-analysis, might also be explained by sleep architecture impairments amplified by a foreign sleep environment. Nevertheless, since the observed in-hospital AHI differences did not reach statistical significance on a group level, this assumption remains speculative. In contrast to several papers included in this review,^{5 18 24 35} OSA severity showed no influence on NtNV of respiratory events on a group level. Based on the individual patient data, Stöberl *et al*⁵ reported the ODI variability to be the higher between ODI 10 and 30 events per hour compared with severe OSA. This association can easily be overseen on a metalevel. Nevertheless, this systematic review and meta-analysis was not supposed to be an individual patient data meta-analysis.

Although we could not demonstrate clinically relevant NtNV between two sequential nights on a group level, our data suggested significant intraindividual variability of respiratory events. As such, night-to-night changes of respiratory parameters (AHI, ODI or RDI) higher than 10/hour were observed in 41% of the patients. Moreover, this intraindividual NtNV happens to be responsible for OSA severity class changes in up to 49% of patients with suspected OSA. Up to 12% of patients might have been missed with a single night measurement, depending on the applied AHI threshold. Considering that the study participants were symptomatic with an average ESS of 11.8, these data suggested that more than 1 in 10 patients would not have got access to therapy for symptomatic OSA based on a diagnostic workup using only one sleep study.

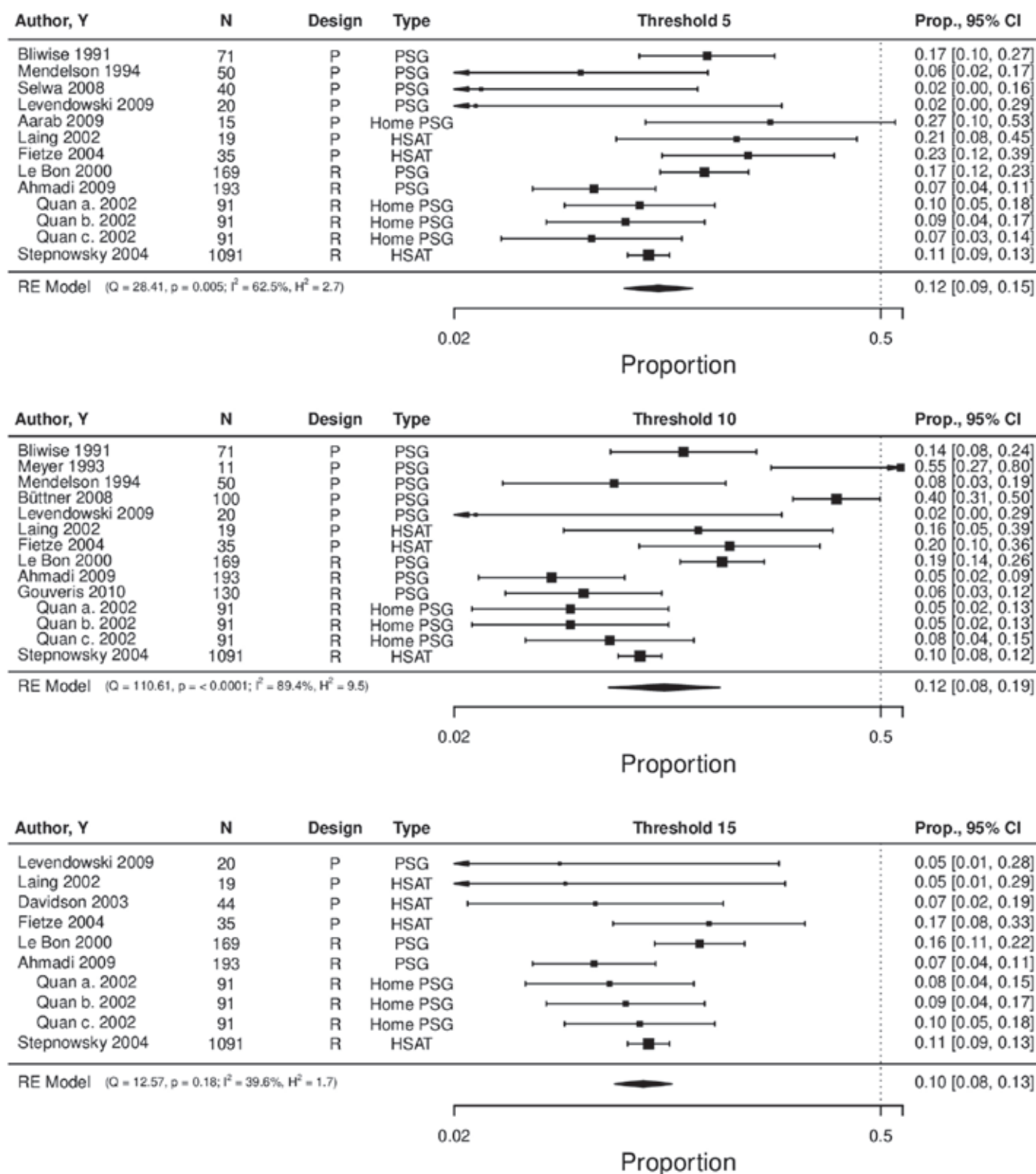


Figure 5 Forest plot of proportion of patients that would have been missed in the first study night due to single-night testing. AHI 5/hour: Kendall's $\tau = -0.180$, $p = 0.435$, AHI 10/hour: Kendall's $\tau = 0.133$, $p = 0.510$, AHI 15/hour: Kendall's $\tau = -0.200$, $p = 0.484$. AHI, Apnoea-Hypopnoea Index; HSAT, home sleep apnoea testing; n, number of analysed patients; PSG, polysomnography; p, prospective study design; Q, Cochran's Q test; Quan a., part of the study by Quan *et al*⁶ referring to data obtained with an RDI including the number of apnoeas plus hypopnoeas each associated with at least a 3% desaturation, Quan b. = part of the study by Quan *et al*⁶ referring to data obtained with an RDI including the number of apnoeas plus hypopnoeas each associated with at least a 4% desaturation, Quan c., part of the study by Quan *et al*⁶ referring to data obtained with an RDI including the number of apnoeas irrespective of any oxygen desaturation plus the number of hypopnoeas associated with at least a 4% desaturation, R, retrospective study design; RE, random effect; RP, respiratory polygraphy; Y, year.

The AASM taskforce also meta-analysed the intraindividual variability of AHI reported in three observational studies assessing the number of OSA diagnosis that would have been missed if one instead of two consecutive PSGs were performed. by copyright. They identified that 9.9%–25% of subjects crossed the AHI threshold of 5/hour in the second sleep study. Using a diagnostic threshold of 5/hour, we found that 9%–15% of the participants crossed the threshold from below 5/hour to over 5/hour in one of the sleep studies only. The smaller CI in our analysis is mainly driven by a retrospective observational study with 1091 patients.⁷ The

small intraindividual NtNV in this study might have been due to the fact that these sleep studies were conducted at home.

Considering the high rate of missed OSA diagnosis and severity class changes due to single-night testing, the singlenight sleep study protocol in the process of OSA diagnosis and staging may have to be revised. How many nights are needed to diagnose OSA with high accuracy can not be answered by this meta-analysis and should be subject of further research. Besides increasing direct costs for the healthcare system, a diagnostic protocol with two or more sleep stu-

dies harbours potential disadvantages. First, an increasing number of sleep studies could lead to an increased false positive diagnosis rate and therefore unnecessary treatment. At second, a multiple night protocol potentially increases patient discomfort, since not all patients might be willing to undergo longitudinal sleep monitoring. Our results may have also major implications on sleep research, fostering the use of multiple sleep night protocols for investigating the potential effect of interventions on respiratory parameters. Investigators should consider that a remarkable number of patients seem to fluctuate with more than 10/hour respiratory events per hour from night to night when assessing the effect of interventions on sleep apnoea severity.

This review and meta-analysis has some limitations. The pooled results were derived mostly from non-interventional observational studies. These are study types in which a lower overall strength of evidence is expected. Furthermore, the bias assessment revealed that three studies showed high risks of bias. Nevertheless, in a sensitivity analysis of the primary outcome, the overall estimate was robust when high risk of bias studies were excluded.

Furthermore, we included studies using different sleep study devices and different scoring rules, which might lead to possibly different AHI, ODI or RDI scorings among these studies. However, including only studies that exactly followed the same protocol regarding used devices, scoring rules, sleep environments and bias assessment, would have minimised the number of included papers and would have led to a substantial loss of information of clinical relevance and statistical power.

Moreover, all studies used validated devices. For example, Prasad *et al* used the Embletta PDS device.⁴⁰ The AHI obtained by the Embletta correlates closely with that obtained by PSG (Pearson correlation, $r=0.979$, $p<0.001$).⁵¹ As a result, we are convinced that the natural course of the nightly change of the AHI in this study should be considered comparable with other studies presenting PSG driven AHI values. Furthermore, we have confidence in our results, since only studies that were consistent in used device type and scoring rules throughout the trial were eligible for this meta-analysis. In addition, the clinical implication remains consistent, as a patient with AHI/ODI/RDI below five events per hour would not receive OSA treatment regardless of the used measurement setup. Another limitation of our study is that whenever studies did not report the mean and SD of relevant parameters, but instead reported median and IQR or range, we recalculated the mean and SD following specific formulas suggested by Wan *et al*.²⁶ While this approach is common, specifically in meta-analyses of observational studies, we cannot be sure if these values would truly have been observed. The quality assessment of the included papers revealed that only one study reported a priori sample size calculation. Most of the included studies were observational studies with only 66.7% following a prospective study design. Furthermore, only a minority of studies controlled for possible confounders such as the intake of alcohol and sedative drugs, both well-known factors that might have influenced NtNV.⁵²

There was a considerable heterogeneity for OSA pretest probability and severity, since some studies included patients with already diagnosed OSA and others included patients with suspected OSA. Nevertheless, we showed that OSA severity was not a statistically relevant moderator for NtNV of respiratory events on a group level.

The primary outcome of this study is based on the assessments of only two recording nights. This is mostly driven by the fact that only eight studies reported results on more than two sleep studies. Considering that the intraindividual variability seemed to increase accordingly with the number of nights, we might have underestimated the NtNV of respiratory events in this meta-analysis. For instance, Stöberl *et al*⁵ conducted their study with the highest number of recording nights (13 nights of pulse oximetry) and reported that only 22% of the patients with moderate-to-severe OSA did not change OSA severity class.

Furthermore, moderators were only assessed on NtNV of mean AHI on a group level. Thus, this analysis could not assess which factors might have influenced the intraindividual NtNV. In addition, sleeping in supine position was originally considered as a moderator variable, but the number of studies reporting on it was only four. In combination with outcomes, the number of studies considered was further reduced. Consequently, this analysis could not evaluate the influence of different sleep positions on NtNV of respiratory events.

Laing and Fichter³⁷ reported on the impact of additional measurement nights on sensitivity in the diagnostic process of OSA, evalua-

ting the accuracy of three sleep studies using a portable sleep monitor. Considering that all 19 evaluated patients had OSA, the sensitivity increased from 52.6% to 73.7% by adding the result of the second night to the first using an AHI threshold of 5/hour. Nevertheless, further research assessing the accuracy of additional sleep study nights is necessary. Finally, there is a need for comparative effectiveness studies in order to determine the effect of repeated sleep studies on clinical outcomes like subjective sleepiness, quality of life, blood pressure and cost-effectiveness.

Contributors MR and MK conceived of the idea for this review. MR, EIS, TG and UH wrote the protocol, MR and MB performed the data extraction. TG and ST did the quality assessment. UH, MR and MB did the statistical analysis. MR, MB, EIS, TG and MK interpreted the statistical results. MR and MB wrote the first draft of the manuscript. All authors revised and approved the final manuscript. MR and MB shared the first authorship.

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A eficácia de palivizumab em mundo real: um estudo populacional em Ontário, Canadá, 1993-2017

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RESUMO

Objetivo Avaliar a eficácia de dois programas de palivizumab dirigidos a crianças de alto risco, definidos por prematuridade, diagnóstico de comorbidades e geografia, e avaliar as potenciais disparidades por rendimento de zonas residenciais.

Conceção do estudo Controlado, séries temporais interrompidas.

Local Ontário, Canadá.

Doentes Utilizámos bases de dados administrativas demográficas e sanitárias interligadas para identificar todas as crianças nascidas em hospitais entre 1 de janeiro de 1993 e 31 de dezembro de 2016. O seguimento terminou no início do segundo aniversário ou a 30 de junho de 2017.

Intervenção Elegibilidade de palivizumab: a criança com nascimento muito prematuro e com ≤ 6 meses de idade durante a época do vírus sincicial respiratório (VSR), < 24 meses de idade com doença pulmonar crônica significativa ou doença cardíaca congênita, ou ≤ 6 meses, de nascimento prematuro ou residentes em regiões remotas.

Principais resultados Doença grave relacionada com VSR, definida como hospitalização ou morte com um diagnóstico de bronquiolite, pneumonia VSR ou VSR.

Resultados Foram identificados 3 milhões de nascimentos e 87 000 eventos relacionados com VSR. Durante o período do estudo, as taxas de doenças graves relacionadas com VSR diminuíram 65,4% entre o grupo de maior risco, as crianças elegíveis < 6 meses (230,6 para 79,8 admissões por 1000 crianças-anos). Relativamente a alterações entre bebés não elegíveis < 6 meses, as taxas diminuíram 10,4% (95% IC -18,6% a 39,4%) entre as crianças elegíveis imediatamente após a introdução de um programa nacional de palivizumab em 1998. Inicialmente, as taxas eram consideravelmente mais elevadas entre crianças de zonas residenciais de baixos rendimentos, mas as taxas específicas de rendimentos convergiram ao longo do tempo entre crianças elegíveis < 6 meses. Esta convergência não foi observada entre outras crianças.

Conclusões A incidência de doenças graves relacionadas com VSR diminuiu durante o período do estudo. Embora não possamos atribuir causalidade, o momento e a magnitude destes declínios sugerem o impacto do palivizumab na redução da carga de VSR e na diminuição das desigualdades sociais entre as crianças elegíveis para palivizumab.

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of respiratory tract infection and hospitalisation among children globally, causing over 33 million episodes of illness and 3 million hospitalisations annually.^{1–3} Approximately 20% of pneumonia and 90% of bronchiolitis cases among children under 6 months of age are attributable to RSV.^{4–6} RSV infection also has long-term health impacts, such as increased risk of asthma.⁷ In the current absence of a vaccine, RSV-related illness can be prevented through immunoprophylaxis.^{8,9} Among children born prematurely without congenital diseases, palivizumab has been found to reduce RSV-related hospitalisations by 80%–85%.^{10–13} Universal prophylaxis is currently not considered cost-effective given annual costs of administering a complete series typically exceed \$6000 (\$CAD) per child.¹⁴ Consequently, palivizumab is offered only to children at greatest risk of severe

What is already known on this topic?

- In the absence of a vaccine, severe respiratory syncytial virus (RSV)-related illness can be prevented through antibody prophylaxis with palivizumab.
- Several authors have highlighted that not all children eligible for palivizumab receive treatment or adhere to the monthly dosing schedule necessary for therapeutic effectiveness.
- While proven efficacious in clinical trials, research evaluating palivizumab's real-world effectiveness is lacking through populationbased effectiveness studies.

What is already known?

- Rates of severe RSV-related illness substantially declined among high-risk infants since palivizumab was introduced in Ontario in 1998.
- Declines in RSV-related admissions among palivizumab-eligible infants were clinically meaningful, but not statistically significant compared with palivizumab-ineligible infants, suggesting reduced effectiveness compared with clinical efficacy.
- We observed a convergence of social inequities in RSV-related admissions among palivizumabeligible children < 12 months old, suggesting that publicly funded palivizumab may help reduce social inequities.

RSV-related illness. Most professional organisations, such as the American Academy of Pediatrics and Canadian Pediatric Society, recommend palivizumab for children who are very young during RSV season (eg, < 12 months) and born extremely to very preterm or diagnosed with serious lung or heart disease.^{11,15}

There is rich evidence to support palivizumab's efficacy¹² but limited real-world evaluation of effectiveness through population-based studies. Given that receipt requires approval from an administering body and monthly doses are needed throughout the RSV season to maintain therapeutic effectiveness, not all children who qualify receive palivizumab or adhere to the burdensome dosage schedule. Prior studies have shown that characteristics predicting severe RSV-related disease may also predict palivizumab nonadherence.^{16,17} Travel, culture, inconvenience and lack of understanding of RSV severity are also recognised barriers.^{8–10} A recent systematic review identified a wide range in palivizumab com-

pliance (25%–100%).¹⁸ In a recent Canadian study, adherence with a full palivizumab series was 81% and adherence was greater among younger children, those with siblings and highly educated or non-smoking mothers.¹⁷ Critically, even within universal healthcare systems, children from low socioeconomic backgrounds experience reduced access to healthcare services and interventions, such as palivizumab.^{16 17}

Our objective was to conduct a population-based evaluation of the impact of the introduction of two palivizumab programmes on severe RSV-related illness occurring before a child's second birthday using the comprehensive health administrative and demographic databases available for all children born in Ontario, Canada during 1993–2016. Specifically, we investigated changes following the introduction of Health Canada's national Special Access Program (SAP) for palivizumab in 1998 and, following licensure in 2002, the Ontario Ministry of Health's Palivizumab Program for High-risk Infants. We hypothesised that the greatest reductions would be observed within children at greatest risk of severe RSV-related illness, namely palivizumab-eligible infants <6 months-old. We also explored social disparities in palivizumab's impact by assessing differences across neighbourhood income levels.

METHODS

Study population and follow-up

We identified all hospital births occurring in Ontario between 1 January 1993 and 31 December 2016. Health outcomes were identified until the earliest of death, second birthday, moving out of province or 30 June 2017 (end of follow-up).

Data sources

We used several linked population-based administrative health and demographic databases. Births were identified using a provincial birth registry, MOMBABY.¹⁹ RSV-related admissions were identified from the Canadian Institute for Health Information's Discharge Abstract Database (DAD) and deaths from the provincial death registry, Ontario's Registrar General Death File (ORG-D). Demographic characteristics were determined from MOMBABY, Census, and Immigration, Refugees and Citizenship Canada (IRCC) Permanent Resident databases. These datasets were linked using unique encoded identifiers and analysed at ICES (formerly the Institute for Clinical Evaluative Sciences).

Outcomes

All RSV-related hospitalisations and deaths were identified, representing a composite measure of severe RSV-related illness. RSV-related hospitalisations were those with an RSV-related diagnostic code identified anywhere on the discharge record based on an algorithm recently validated among Ontarian infants by Pisesky *et al.*²⁰ Specifically, the following International Classification of Diseases 10th and 9th revision (ICD-10 and ICD-9) codes were considered: RSV pneumonia (J12.1, 480.1); acute bronchiolitis (J21.1, 466.1); or RSV as the cause of disease classified elsewhere (B97.4, 079.6). Similarly, RSV-related deaths were those with the above RSV-related codes identified on the death certificate. Since causes of death are routinely undercoded, to increase sensitivity, we also considered all non-accidental deaths occurring within 30 days of an RSV-related hospitalisation, as done previously.²¹

Eligibility for federal and provincial palivizumab programmes

Palivizumab eligibility criteria have periodically changed in Ontario; in recent years, a risk scoring tool has been used to assess preterm infants, incorporating factors such as daycare, household crowding and tobacco smoke exposure.²² Such information is not available through administrative data and, currently, there is no identifier for palivizumab receipt. Given challenges in accurately identifying these characteristics and to maximise transferability to other settings with stricter eligibility criteria, we created a three-level variable for children clearly eligible, possibly eligible and clearly ineligible for palivizumab based on standard criteria consistently applied throughout the study period.^{22–24}

Clearly eligible children were: (1) born ≤32 weeks gestational age (wGA) and aged ≤6 months during RSV season (ie, mid-November through March); (2) <24 months with bronchopulmonary dysplasia; (3) <24 months with hemodynamically significant congenital heart disease or (4) born 33–36 wGA, aged ≤6 months during RSV season

and living in isolated communities where hospital care is not readily accessible. Possibly eligible children were aged <24 months and previously diagnosed with other congenital heart disease, congenital airway anomalies, or Trisomy 21, and all other preterm (33–36 wGA) infants ≤6 months during RSV season. Additional details are provided in online supplementary appendices A–C.

Covariates

Given the absence of gestational age data in ICD-9, gestational age groups were determined for all births using a validated algorithm.^{25 26} Major congenital anomalies were identified from any hospitalisation occurring before the second birthday with ICD-9/10 codes of 740–59 or Q00–99.²⁷ Presence of hemodynamically significant congenital heart disease was determined on the basis diagnostic and procedural codes occurring before the second birthday.²⁸ Rurality was operationalised using the Rurality Index of Ontario (RIO), a continuous measure created for policy purposes.²⁹ Geographic isolation was defined as RIO ≥75, following funding incentives for isolated communities.²⁹ Neighbourhood-level income quintile was measured at the dissemination area, Canada's smallest census area consisting of 400–700 persons. Due to small cell sizes, income was dichotomised in analysis: quintiles 5 and 4 as high-income and quintiles 1 and 2 as low-income.

Statistical analyses

We modelled annual rates of severe RSV-related illness using Poisson regression, including an offset term for log person-time to calculate rates. Years were defined as 1 July through 30 June to capture unique RSV seasons. An interrupted time series design was conducted using a segmented regression approach to assess both step and slope changes following the introduction of each programme: the national SAP in 1998 and the provincial highrisk program in 2002.³⁰

In the secondary analysis of socioeconomic differences by income, we stratified models according to palivizumab eligibility. Given statistical power limitations, we only considered step and slope changes over the entire study period and not by programme.

All analyses were stratified by age at infection: <6, 6–11 and 12–23 months. Analyses were performed in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The study included over 3 million births, with 86 772 RSV-related hospitalisations, accounting for 238026 bed-days and 58 RSV-related deaths observed among 77323 children. Bronchiolitis was the most common diagnosis identified among children with severe RSV-related illness (95.2%); 4.6% had a diagnosis of RSV pneumonia and 2.1% had an RSV confirmation recorded on their discharge record. In all, 1.1% of included children were considered clearly palivizumab-eligible and another 4.8% possibly eligible (table 1). Only 4.6% of children with severe RSV-related illness met any of the considered palivizumab eligibility criteria (online supplementary table 1).

Rates of severe RSV-related illness were substantially higher among infants <6 months, particularly eligible infants (figures 1 and 2). Over the study period, there was a statistically significant trend towards declining rates of severe RSV-related illness among all age groups; rates of decline significantly differed by age (figure 1).

Among palivizumab-eligible infants <6 months, the absolute decline in rates was 65.4% (51.4% to 75.4%) over the study period; in contrast, declines of 41.1% (28.4% to 51.5%) and 31.1% (26.0% to 36.0%) were observed among possibly eligible and ineligible infants <6 months. Among eligible infants <6 months, absolute declines of 18.3% (–9.9% to 46.6%) and 6.7% (–16.6% to 29.9%) occurred the year following the national and provincial programmes (figure 2). Relative to changes among ineligible infants <6 months old, rates dropped an additional 10.4% (–18.6% to 39.4%) among eligible infants (<6 months) immediately following palivizumab's introduction in 1998; that is, the 'level change' among palivizumab-eligible children was –18.3% (–46.6 to 9.9) while the 'level change' among palivizumab-ineligible children was –7.9% (–14.7 to 1.2), resulting in a relative 'level change' of –10.4 (–39.4 to 18.6) among palivizumab-eligible infants, compared with palivizumab-ineligible infants (online supplementary table 2). Relative to changes within ineligible infants, the improvement in RSV rates observed after the first introduction of palivizumab among palivizumab-eligible infants was not statistically significant.

Within the 6–11-month-old age group, rates of severe RSV-related illness dropped an additional 23.1% (–18.6% to 64.8%) for eligible infants relative to ineligible infants immediately following palivizumab's first introduction in 1998 (online supplementary figure 1 and table 2); however, RSV rates increased 39.9% (5.7% to 74.1%) relative to palivizumab-ineligible infants following palivizumab's licensure in 2002. A similar pattern was observed among children aged 12–23 months (online supplementary figure 2 and table 2). See online supplementary table 2 for full model results.

Among infants <6 months, rates of severe RSV-related illness were substantially greater among those from low-income neighbourhoods (figure 3). For example, during the first study year (1993), rates of severe RSV-related illness were 19.8% greater among eligible infants <6 months from low-income neighbourhoods, compared with their high-income counterparts (246.7 vs 197.9 admissions per 1000 child-years). However, among eligible infants <6 months, this income difference narrowed by 1.8% per year on average ($p=0.0423$), with rates converging during the final 4 years of the study. Specifically, RSV rates declined 4.9% per year on average ($p<0.0001$) among clearly eligible, low-income infants <6 months; compared with 3.1% among high-income infants ($p<0.0001$). This gap widened, but not significantly so, among possibly eligible infants <6 months. Among palivizumab-ineligible infants <6 months, this income gap significantly diminished but did not converge. Similar patterns were observed among 6–11-month-olds, though no changes were statistically significant and inequities were less apparent (online supplementary figure 3). No clear income disparities were apparent among 12–23-month-olds (online supplementary figure 4). Full model results are presented in online supplementary table 3.

DISCUSSION

In this large, population-based study, rates of severe RSV-related illness declined substantially over the 24-year study period. The greatest improvements were observed among palivizumab-eligible infants <6 months; however, these changes were not statistically significant relative to changes within ineligible infants. Further, we observed that rates of severe RSV-related illness were initially greater among infants <12 months from low-income neighbourhoods, regardless of eligibility, but these disparities diminished among eligible infants over time. While we cannot definitively attribute these effects to the availability of palivizumab, the timing is suggestive of its impact. These observations are consistent with palivizumab efficacy demonstrated in trials and suggest that this efficacy does translate into substantial real-world effectiveness,³¹ although to a lesser degree.

There is rich evidence supporting palivizumab's efficacy in various clinical subgroups;^{9,32} however, there has been scant research into real-world effectiveness. To our knowledge, this is the first population-based evaluation of any palivizumab programme, so there are no comparative studies. However, two US population-based studies have reported on RSV-related admissions over the past two decades and a third on bronchiolitis admissions;^{33–35} none explicitly evaluated changes due to palivizumab. A 55% decline in RSV-related hospitalisations was observed over 1998–2011 among Californian infants <12 months with high-risk medical conditions (7.6–3.4 per 1000 children), compared with 43% among those without any high-risk conditions.³³ Similarly, a 12% decline in RSV-related admissions was observed among US infants <2 years old over 1998–2012; declines of 38% and 10%, respectively, occurred among children with and without high-risk conditions.³⁴ Further, a 17% decline in bronchiolitis-related admissions was reported over 2000–2009 among US children <2 years old.³⁵

Considering the multitude of steps required to receive a full series of palivizumab (eg, parental/provider knowledge of eligibility, administering approval and adherence), effectiveness studies are critical for determining real-world impact. Even within clearly eligible, high-risk infants, real-world effectiveness of these palivizumab programmes was not comparable to trial-based efficacy estimates.^{3,10} The relative decline in severe RSV among eligible infants <6 months was 65.4% over our study period, with the greatest impact seen immediately following palivizumab's first introduction in 1998. In contrast, RSV rates declined 41.1% and 31.1%, respectively, over the study period among possibly eligible and ineligible infants <6 months. Improvements were less apparent among older children, for which fewer RSV events occur and palivizumab eligibility criteria are more restrictive.

Ontario's criteria are considerably comprehensive; most jurisdictions limit palivizumab to young infants born very preterm and with severe heart or lung disease (online supplementary appendix D).^{24,36} Thus, additional research is required to ascertain the effectiveness of palivizumab programmes in other settings. While we observed clinically meaningful declines in severe RSV among palivizumab-eligible infants, we also observed declines among palivizumab-ineligible infants and the difference between these two groups was not statistically significant. Declines in severe RSV among palivizumab-ineligible children could reflect changes in RSV dynamics, prevalence of cofactors influencing severity of infection (eg, parental smoking) or other factors.¹⁶ Both population-based studies of US infants found substantial reductions in RSV-related admissions among low-risk infants, further suggesting improvements beyond palivizumab.^{33,34}

An additional key finding was that the initial gap in RSV-related illness among eligible infants <6 months from high-income vs low-income neighbourhoods entirely diminished over time. While we are unable to attribute this finding definitively to equitable access to palivizumab, the timing is consistent with such an underlying mechanism. This finding is encouraging given that the introduction of novel interventions frequently accentuates health disparities via preferential uptake by the most advantaged.^{37,38} While multiple studies have shown that children from lower socio-economic backgrounds have increased RSV-related hospitalisation rates, none to our knowledge have explicitly investigated changes in these inequities.^{16,33,37}

While the strengths of this study are related to its population-based nature, these data have limitations. We were unable to determine palivizumab receipt or comprehensively identify all eligibility criteria. However, the distribution of children meeting eligibility criteria in our study was comparable to the Canadian Registry of Synagis (CARESS) (online supplementary table 4).³⁹ Further, in 2015/2016, 3119 children received palivizumab in Ontario;⁴⁰ nearly 2000 children would have been clearly palivizumab-eligible in our study. Moreover, even though we included all severe RSV-related illness among all children born in Canada's largest province over multiple decades, we may lack power to detect true differences within eligible groups, particularly older children for which RSV events were rare and few are palivizumab-eligible. We were also unable to ascertain laboratory confirmation of RSV. Given viral tests are inconsistently performed as there are no provincial testing guidelines for RSV, limiting the outcome to laboratory-confirmed RSV would have underestimated the true burden of RSV and biased our results. Similarly, biases in admission practices should be considered; for example, clinicians may be more prone to admit younger children or children with underlying complexities compared with older or less fragile children with a similar level of respiratory distress. In addition to age-stratifying our results, we attempted to further investigate some of these differences, for example, by investigating supplemental oxygen and ventilation use. Unfortunately, diagnostic and procedure codes for these diagnoses/interventions were not consistently available or applied throughout the ICD-9 and ICD-10 eras, limiting our ability to accurately investigate these outcomes over the entire study period and, particularly, during the prepalivizumab (ie, ICD-9) era. These coding considerations also limit ability to look at other changes in practice which may explain part of the decline in RSV-related admissions over the study period; for example, children who were sent home with oxygen therapy to prevent an admission. Moreover, some bronchiolitis admissions would have been due to other pathogens, for example, influenza; however, approximately 85% of bronchiolitis in children are attributable to RSV.^{1,2,6,20}

The major strengths of this study include the ability to study trends at a population-level over a 24-year period. We also incorporated control groups (ie, palivizumab ineligible and possibly eligible children) to account for secular trends not directly influenced by palivizumab, such as changes in medical coding, practice, admissions and cofactors. Controlled interrupted time series analysis with preintervention and postintervention periods are considered the most rigorous quasiexperimental design.³⁰ Nevertheless, these estimates are likely conservative given data limitations

CONCLUSION

This large, population-based study spanning multiple decades found that severe RSV-related illness substantially declined among high-risk infants in Ontario, Canada. While we cannot firmly attribute causality, the magnitude and timing of changes, along with diminished social

Table 1 Characteristics of children included in the study, that is, all births in Ontario occurring 1 January 1993 to 31 December 2016, stratified by palivizumab eligibility group

Characteristic	Ineligible N n=2837145	%	Possibly eligible N n=143913	%	Eligible N n=34301	%
Birth year						
1993–1996	462 235	16.29	22 377	15.55	7015	20.45
1997–2000	443 707	15.64	23 284	16.18	6732	19.63
2001–2004	464 534	16.37	23 595	16.40	5670	16.53
2005–2008	494 542	17.43	24 291	16.88	5197	15.15
2009–2012	487 847	17.19	24 607	17.10	4939	14.40
2013–2016	484 280	17.07	25 759	17.90	4748	13.84
High risk birth month (November–January)	655 754	23.11	42 315	29.40	9832	28.66
Sex (female)	1 387 750	48.91	65 046	45.20	15 317	44.65
Multiple birth	53 151	1.87	28 868	20.06	7473	21.79
Estimated wGA						
<28 wGA (extremely preterm)	1753	0.06	261	0.18	11 338	33.05
28–32 wGA (very preterm)	2973	0.10	377	0.26	15 408	44.92
33–36 wGA (preterm)	30 620	1.08	131 800	91.58	2095	6.11
37+ wGA (term)	2 763 110	97.39	10 935	7.60	5309	15.48
Missing	38 689	1.36	540	0.38	151	0.44
Weight group						
<1500 g	4337	0.15	2852	1.98	22 672	66.10
1500–1999 g	6562	0.23	25 261	17.55	4360	12.71
2000–2499 g	70 582	2.49	45 815	31.84	1251	3.65
2500–2999 g	423 850	14.94	42 265	29.37	1823	5.31
3000–3499 g	1 069 534	37.70	20 878	14.51	2201	6.42
3500–3999 g	902 861	31.82	5147	3.58	1390	4.05
4000–4499 g	301 482	10.63	1253	0.87	470	1.37
4500 g +	57 937	2.04	442	0.31	134	0.39
Mean weight, g (SD)	3438.42	503.43	2495.50	579.44	1512.84	958.70
Congenital diseases†						
Any major congenital anomaly	49 968	1.76	19 550	13.58	13 137	38.30
CHD	0	-	13 453	9.35	11 239	32.77
Hemodynamically significant CHD	0	-	0	-	6596	19.23
Other CHD	0	-	13 453	9.35	4643	13.54
Major congenital airway anomaly	0	-	1980	1.38	349	1.02
Other clinical diagnoses†						
Bronchopulmonary dysplasia/ chronic lung disease	0	-	0	-	4311	12.57
Trisomy 21	0	-	1044	0.73	173	0.50
Sociodemographic characteristics*						
Mother's immigration status						
Canadian born	2 207 476	77.81	112 047	77.86	26 804	78.14
Long-term resident, 5+ years	332 367	11.71	17 810	12.38	4176	12.17
Short-term resident, <5 years	293 622	10.35	13 837	9.61	3261	9.51
Refugee	3680	0.13	219	0.15	60	0.17
Maternal age						
<18 years	64 765	2.28	3743	2.60	1081	3.15
19–24	428 232	15.09	21 141	14.69	5385	15.70
25–29	828 752	29.21	38 524	26.77	9300	27.11
30–34	969 408	34.17	47 281	32.85	10 761	31.37
35–39	458 174	16.15	26 592	18.48	6192	18.05
40+	87 758	3.09	6626	4.60	1579	4.60
Mean maternal age (SD)	29.73	5.44	30.13	5.79	29.88	5.93
Neighbourhood income quintile						
1 (lowest 20% income)	626 463	22.08	33 814	23.50	442	1.29
2	567 822	20.01	29 532	20.52	8575	25.00
3	568 979	20.05	28 662	19.92	7193	20.97
4	581 546	20.50	28 524	19.82	6603	19.25
5 (highest 20% income)	467 644	16.48	22 175	15.41	6530	19.04
Missing	24 691	0.87	1206	0.84	4958	14.45
Residence at time of birth						
Urban	2 518 452	88.77	129 573	90.04	30 057	87.63
Rural	307 202	10.83	13 763	9.56	4047	11.80
Missing	11 491	0.41	577	0.40	197	0.57
Geographically isolated residence	23 391	0.82	97	0.07	1041	3.03

Statistically significant difference between eligibility groups noted across all characteristics; $p < 0.0001$.

*Determined at the time of birth.

†Diagnosed before second birthday.

BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CLD, chronic lung disease; wGA, weeks gestational age.

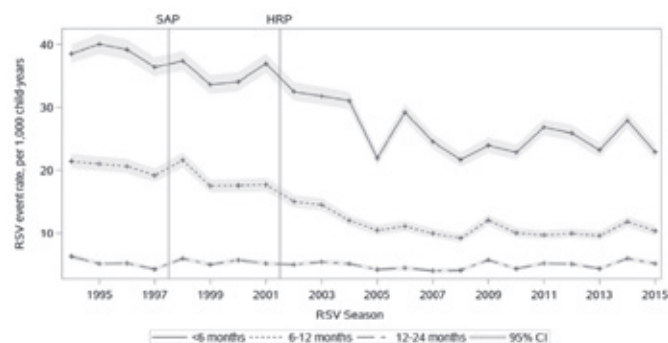


Figure 1 Annual rates (95% CI) of severe RSV-related illness* among all children born in Ontario, 1 January 1993 to 31 December 2016, stratified by age at infection. Average annual change (95% CI) was -2.6% (-2.8 to -2.5), -4.5% (-4.7 to -4.8) and -0.3% (-0.6 to -0.1) for <6 , 6–11 and 12–23 month-olds, respectively. *Annual rates of RSV related hospitalisation or death for 1 July through 30 June inclusive.

HRP, Provincial High-Risk Palivizumab Program (2002); RSV, respiratory syncytial virus; SAP, National Special Access Palivizumab Program (1998).

inequities, among palivizumabeligible infants are noteworthy. While there is rich evidence to support the clinical efficacy of palivizumab, this work provides much needed insights into the real-world effectiveness of palivizumab programmes, which appear to have reduced effectiveness compared with clinical trial estimates. Additional research is required to determine whether, and to what degree, the effectiveness of palivizumab programmes could be enhanced through ensuring therapeutic levels are maintained throughout RSV season (ie, adhering to the monthly dosing schedule) and efforts to promote the availability and uptake of palivizumab among eligible children, particularly where publicly funded.

Contributors TF conceptualised the study, analysed the data, interpreted the findings and drafted the manuscript. JDM contributed critically to study design, methods, interpretation and the final manuscript. TAS provided statistical guidance, assisted with statistical interpretation of the results and critically contributed to the final manuscript. ASW created the dataset for analysis and critically contributed to the final manuscript. JCK and DF contributed critically to study design, interpretation and the final manuscript. AG supervised the study design, provided clinical context for study methods and findings and critically contributed to the final manuscript. All authors approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethics approval was obtained from the University of Toronto and Hospital for Sick Children Research Ethics Boards.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors on request, understanding that the computer programs may rely on coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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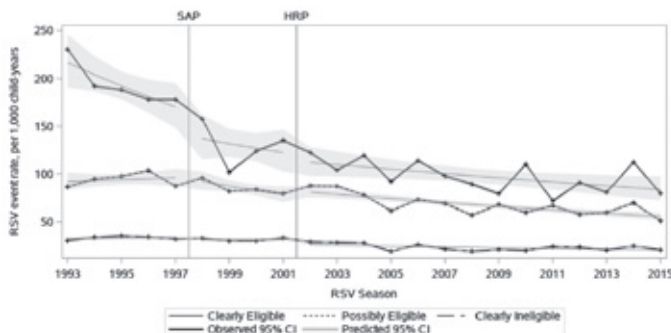


Figure 2 Annual observed and predicted rates (95% CI) of severe RSV-related illness* among infants under 6 months of age†, according to eligibility for Ontario's palivizumab programme; 1993–2016. *Annual rates of RSV-related hospitalisation or death for 1 July through 30 June inclusive. † <6 months of age at the time of admission/death. Model parameter estimates, along with associated 95% CIs and p values, are provided in online supplementary table 2. HRP, Provincial High Risk Palivizumab Program (2002); RSV, respiratory syncytial virus; SAP, National Special Access Palivizumab Program (1998). Protected by copyright.

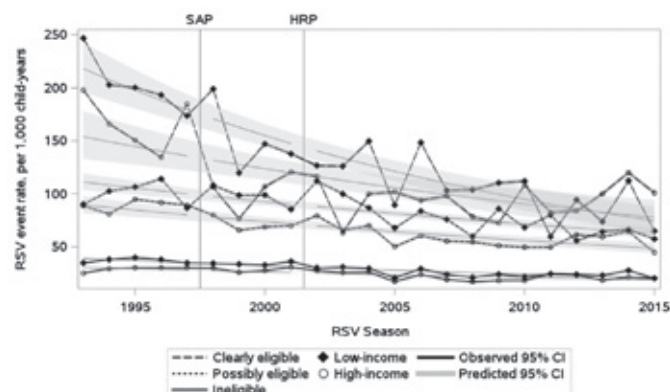


Figure 3 Annual observed and predicted rates (95% CI) of severe RSV-related illness* among high-income vs low-income infants under 6 months of age**, stratified by palivizumab eligibility. *Annual rates of RSV-related hospitalisation or death for 1 July through 30 June inclusive. ** <6 months of age at the time of hospitalisation/death. Annual rate of change between high-income and low-income groups: -1.78 ($p=0.0423$), 0.16 ($p=0.7500$) and -0.60 ($p=0.0009$), respectively, for clearly eligible, possibly eligible and ineligible groups. Model parameter estimates, along with associated 95% CIs and p values, are provided in online supplementary table 3. HRP, Provincial High-Risk Palivizumab Program (2002); RSV, respiratory syncytial virus; SAP, National Special Access Palivizumab Program (1998).

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Risco de osteoporose e fraturas de fragilidade na asma devido a corticosteróides orais e inalatórios: dois estudos de controlo de caso de base populacional

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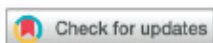
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RESUMO

Contexto Os corticosteróides inalatórios (CI) e orais (CO) são amplamente utilizados na asma. Contudo, o risco de osteoporose e fratura de fragilidade (FF) devido aos corticosteróides para o tratamento da asma ainda não está bem estabelecido.

Métodos Realizámos dois estudos de controlo de caso utilizando dados interligados das bases de dados *Clinical Practice Research Datalink* (CPRD) e *Hospital Episode Statistics* (HES). Utilizando uma coorte de asma, identificámos separadamente doentes com osteoporose ou FF e controlos equiparados para género, idade e prática clínica. Utilizou-se uma regressão logística condicional para determinar a associação entre a exposição a CI e CO e o risco de osteoporose ou FF. Também foi calculada a prevalência de doentes que receberam pelo menos um bisfosfonato.

Resultados Verificou-se uma relação dose-resposta entre a dose cumulativa e o número de prescrições de CO/CI no ano anterior e o risco de osteoporose ou FF. Após o ajustamento para confundidores, as pessoas que receberam mais prescrições de CO (≥ 9 vs. 0) sentiram um aumento de 4,50 (95% IC 3,21 a 6,11) no risco de osteoporose e de 2,16 (95% IC 1,56 a 3,32) no risco de FF. Para CI (≥ 11 vs 0), os OR foram de 1,60 (95% IC 1,22 a 2,10) e 1,31 (95% IC 1,02 a 1,68), respetivamente. A dose cumulativa teve um impacto semelhante, verificando-se que os doentes que receberam mais CO ou CI apresentavam maior risco. A prevalência de doentes a tomar ≥ 9 CO e pelo menos uma prescrição de bisfosfonatos foi de apenas 50,6% para osteoporose e de 48,4% para FF.

Conclusões Os resultados sugerem que a exposição a CO ou CI constitui um fator de risco independente para a saúde óssea em doentes com asma. Recomenda-se a administração de esteróides ao nível mais reduzido possível para manter o controlo da asma.

INTRODUCTION

Asthma is one of the most common chronic, non-communicable diseases affecting around 334 million people worldwide.¹ Inhaled (ICS) and oral (OCS) corticosteroids play a crucial role in the control of airway inflammation in asthma.² The Global Initiative for Asthma (GINA) guidelines suggest a stepwise approach with low- to high-dose ICS alone or in combination with long-acting- β_2 -agonists as the firstline treatment for patients with moderate to severe asthma, and use of OCS for patients experiencing exacerbations or having severe asthma.³ Both ICS and OCS are known to cause well-recognised side effects.^{4–7}

One of the most frequent adverse effects is osteoporosis which can lead to fragility fractures (FF).^{8–10} FF are associated with substantial increased healthcare costs, morbidity and mortality.^{11,12} Studies investigating the adverse effects of corticosteroids on bone health based on change in bone mineral density (BMD) in patients with asthma have contradictory findings. Laatikainen *et al* did not find statistically significant differences in BMD between three groups of patients with asthma (ICS (n=26) vs OCS (n=65) vs non-exposed (n=28)).¹³ Similarly, a 4-year longitudinal study assessing lumbar spine BMD in people with asthma receiving low (n=26) and high (n=9) doses of ICS as well as sporadic (n=26) and frequent (n=9) OCS did not reveal any change in BMD ($p>0.05$).¹⁴ This might be a result due to small

Key messages

What is the key question?

► What is the impact of oral (OCS) and inhaled (ICS) corticosteroid treatment on osteoporosis and fragility fracture risk among people with asthma?

What is the bottom line?

► Exposure to OCS or ICS is an independent risk factor for bone health in patients with asthma. There is a clear dose-response relationship between cumulative dose and prescriptions of OCS/ICS, and risk of osteoporosis and fragility fractures.

Why read on?

► The use of ICS in asthma is likely to increase with the recent change in Global Initiative for Asthma (GINA) guidance recommending combined long-acting- β_2 -agonists with ICS at step 1 and the prescribing of OCS follows an upward trend. Additionally, current guidelines on asthma do not fully cover the management of bone comorbidities and no specific bone protection guidance is given. This large study using primary and secondary care data provides pragmatic guidance to clinicians by stratifying bone health risk by dose, number of prescriptions, and type of OCS and ICS.

sample size in both studies. In contrast, Wong *et al*¹⁵ showed that cumulative dose of ICS (median 876mg) was negatively associated with BMD ($p<0.05$) in young patients with asthma. Sivri *et al*¹⁶ also found a significantly lower BMD in female patients with asthma exposed to regular use of ICS (750 to 1500 μ g/day for at least 3 months). Few studies have quantified the risk between corticosteroids and bone health in patients with asthma, mostly examining the effects of OCS.^{17–19} However, these studies have been limited by their small size and focus on severe asthma.

Given that the use of ICS in asthma is likely to increase with the recent change in GINA guidance recommending combined long-acting- β_2 -agonists with ICS at step 13 and the upward trend in prescribing of OCS,²⁰ we sought to clarify the link between steroids, osteoporosis and FF in patients with asthma, stratifying the risk by dose, number of courses and type of steroids.

METHODS

Source population

We conducted a population-based nested case-control study utilising the Clinical Practice Research Datalink (CPRD) GOLD, a large longitudinal primary care database,²¹ linked to the Hospital Episode Statistics (HES) database.²² We used the July 2018 dataset which covers more than 15.4 million patients from 738 practices

Table 1 Characteristics of patients with osteoporosis and control subjects

Characteristic	Cases (n=1564) N (%)	Controls (n=3313) N (%)	Unadjusted OR (95%CI)
Age* (mean±SD) (years)	69.4±10.7	68.1±10.4	-
Sex			
Male	303 (19.4)	619 (18.7)	-
Female	1261 (80.6)	2694 (81.3)	-
Smoking status			
Never	584 (37.3)	1438 (43.4)	1.00
Former	584 (37.3)	1267 (38.3)	1.17 (1.02 to 1.35)
Current	381 (24.4)	574 (17.3)	1.95 (1.62 to 2.33)
Missing status	15 (0.1)	34 (1.0)	0.93 (0.37 to 2.32)
BMI status (kg/m ²)			
Underweight (<18.5)	76 (04.9)	48 (01.5)	2.25 (1.50 to 3.36)
Normal (18.5–24.9)	481 (30.7)	654 (19.7)	1.00
Overweight (25–29.9)	435 (27.8)	990 (29.9)	0.56 (0.47 to 0.67)
Obese (≥30)	322 (20.6)	1099 (33.2)	0.39 (0.32 to 0.46)
Missing status	250 (16.0)	522 (15.8)	0.63 (0.51 to 0.79)
Alcohol status			
Non-drinker	187 (12.0)	323 (09.8)	1.00
Ex-drinker	181 (11.6)	402 (12.1)	0.81 (0.62 to 1.05)
Current drinker	1052 (67.3)	2315 (69.9)	0.85 (0.69 to 1.04)
Missing status	144 (9.2)	273 (8.2)	1.02 (0.76 to 1.37)
IMD (social class)			
1 (least deprived)	295 (18.9)	653 (19.7)	1.00
2	324 (20.8)	688 (20.8)	1.12 (0.91 to 1.40)
3	318 (20.3)	710 (21.4)	1.13 (0.90 to 1.41)
4	319 (20.4)	665 (20.1)	1.21 (0.96 to 1.53)
5 (most deprived)	306 (19.6)	597 (18.0)	1.36 (1.06 to 1.74)
Charlson Comorbidity Index			
1	717 (45.8)	1847 (55.8)	1.00
2	258 (16.5)	523 (15.8)	1.27 (1.06 to 1.52)
3	274 (17.5)	447 (13.5)	1.51 (1.25 to 1.81)
4	151 (9.7)	250 (7.6)	1.54 (1.21 to 1.94)
≥5	164 (10.5)	246 (7.4)	1.62 (1.27 to 2.06)
Drug use in the year prior to the index date			
Bisphosphonates	851 (54.5)	162 (4.9)	25.11 (19.38 to 32.53)
Vitamin D and/or calcium	418 (26.8)	243 (7.3)	4.47 (3.69 to 5.40)
History of a diagnosis ever prior to the index date			
Fall	450 (28.8)	575 (17.4)	1.95 (1.65 to 2.27)
Any fracture	478 (31.0)	533 (16.1)	2.38 (1.98 to 2.68)

Percentages have been rounded and might not total 100.

*Age at the index date.

BMI, body mass index; IMD, Index of Multiple Deprivation.

across the UK. The percentage of patients is approximately 7% of the UK population and they are representative with respect to age, gender and ethnicity of the wider UK population. HES is a secondary care database consisting of all hospitalisations in England, consequently only 60% of CPRD patients have linked data. The study was approved by the Independent Scientific Advisory Group of the CPRD (ISAC protocol number 19_041RA).

Cohort definition

The study population included all adult patients (≥18 years old) with a Read code for asthma between 1 April 2004 (activation of Quality and Outcomes Framework score) to 31 December 2017, with at least 1 year of data collection prior to the diagnosis of asthma date ensuring that only 'incident' cases were picked.²³ We included patients classed as 'acceptable' research quality data and registered to an up-to standard practice according to CPRD's recommendations.

Cases, controls and outcomes definition

We conducted two nested case-control studies using CPRDlinked HES data, with cases defined by the first-recorded diagnosis of (1) osteoporosis and (2) FF (as separate outcomes). The databases were linked using an identifier variable (same in both databases) called 'patid', and then we looked for the earliest diagnosis in both databases by using either the Read or International Classification of Diseases (ICD-10) code, depending on the database. The date of the first diagnosis of (1) osteoporosis and (2) FF served as the index date for the cases. Each

case was matched with up to four randomly selected patients from the remaining patients with asthma by age (±1 year), gender and practice. We assigned the same index date to controls and cases.

Vertebral, hip, forearm-wrist and humeral fractures are considered common sites of FF, and are associated with morbidity and mortality.^{12,24} A composite of these fracture sites was used to define the presence of FF. Any fracture described as an 'open fracture' was excluded, since this type usually occurs via a high-energy event, and is not related to frailty. The code list was reviewed by a clinician to identify appropriate fractures that were unlikely to be osteoporotic in nature.

Potential confounders

For each participant in this study, we retrieved information on the following variables which are well-established risk for fracture or thought to have an impact on osteoporosis or fracture risk and are also likely to be recorded within the databases: age at the index date; sex, including only those clearly classified as male or female; body mass index (BMI) using the nearest measurement prior the index date and categorised according to the WHO (see online supplemental file); smoking and alcohol status using the nearest measurement ever prior to the index date (see online supplemental file); socioeconomic status measured by using the patient-level Index of Multiple Deprivation (IMD) 2015 in quintiles, with quintile 1 being the least and quintile 5 the most deprived; osteoporosis (only when the outcome was FF), any fracture (not those considered as an outcome) or falls prior the index date; and bisphosphonates, vitamin D and calcium supplements in the year prior the index date. The comorbidities

Table 2 Characteristics of patients with fragility fractures and control subjects

Characteristic	Cases (n=2131) N (%)	Controls (n=4421) N (%)	Unadjusted OR (95%CI)
Age* (mean±SD) (years)	65.1±14.9	64.0±14.1	-
Sex			
Male	633 (29.8)	1215 (27.5)	-
Female	1497 (70.2)	3206 (72.5)	-
Smoking status			
Never	813 (38.2)	1870 (42.3)	1.00
Former	767 (36.0)	1693 (38.3)	1.04 (0.92 to 1.18)
Current	513 (24.0)	806 (18.2)	1.53 (1.32 to 1.77)
Missing status	38 (01.8)	52 (01.2)	1.81 (0.94 to 3.49)
BMI status (kg/m ²)			
Underweight (<18.5)	79 (3.7)	62 (1.4)	2.28 (1.57 to 3.29)
Normal (18.5–24.9)	507 (23.8)	905 (20.5)	1.00
Overweight (25–29.9)	588 (27.6)	1291 (29.2)	0.80 (0.68 to 0.93)
Obese (≥30)	538 (25.2)	1389 (31.3)	0.72 (0.61 to 0.84)
Missing status	419 (19.6)	774 (17.5)	0.95 (0.80 to 1.13)
Alcohol status			
Non-drinker	203 (09.5)	396 (09.0)	1.00
Ex-drinker	211 (09.9)	467 (10.6)	0.91 (0.72 to 1.17)
Current drinker	1506 (70.7)	3156 (71.4)	0.99 (0.82 to 1.20)
Missing status	211 (9.9)	402 (9.1)	1.07 (0.82 to 1.38)
IMD (social class)			
1 (least deprived)	382 (18.0)	893 (20.2)	1.00
2	468 (22.0)	916 (20.8)	1.25 (1.04 to 1.50)
3	442 (20.8)	952 (21.5)	1.16 (0.95 to 1.40)
4	418 (19.7)	819 (18.5)	1.26 (1.04 to 1.55)
5 (most deprived)	420 (19.7)	840 (19.0)	1.23 (1.04 to 1.52)
Charlson Comorbidity Index			
1	1195 (56.1)	2786 (63.0)	1.00
2	319 (15.0)	643 (14.5)	1.17 (0.99 to 1.38)
3	256 (12.0)	460 (10.4)	1.33 (1.11 to 1.59)
4	157 (7.4)	268 (6.1)	1.39 (1.11 to 1.75)
≥5	204 (9.6)	264 (6.0)	1.71 (1.37 to 2.13)
Drug use in the year prior to the index date			
Bisphosphonates	255 (12.0)	217 (4.9)	2.57 (2.10 to 3.15)
Vitamin D and/or calcium	194 (9.1)	260 (5.9)	1.54 (1.25 to 1.91)
History of a diagnosis ever prior to the index date			
Fall	577 (27.1)	607 (13.7)	2.44 (2.11 to 2.81)
Osteoporosis	261 (12.3)	202 (4.6)	2.82 (2.29 to 3.46)
Any fracture	707 (33.2)	662 (15.0)	2.94 (2.57 to 3.36)

Percentages have been rounded and might not total 100.

*Age at the index date.

BMI, body mass index; IMD, Index of Multiple Deprivation.

were also summarised using the Charlson Comorbidity Index score.²⁵ If there was no record for a medication or diagnosis, patients were assumed to have not had the exposure.

Exposure assessment

Corticosteroid use was categorised in a number of ways. Initially, a 1-year period prior to index date was used to identify the exposure status. OCS and ICS use were examined as the number of prescriptions filled. It was not possible to categorise the OCS use by type since 97% of individuals received prednisolone. ICS was grouped according to type as follows: beclomethasone dipropionate, budesonide, fluticasone propionate and ciclesonide. Where the type of ICS was changed during the year, we considered the most frequently prescribed. We also assessed the OCS and ICS as cumulative dose in milligrams (mg) over the previous year. To calculate the cumulative OCS and ICS dose, we used information from tablet strength (eg, 5mg) or the dose of drug delivered with each inhalation (eg, 0.1mg) and prescribed quantity, multiplying the quantity by strength for each prescription, and then all doses per patient were summed. We dealt with missing or implausible values using a recognised algorithm (see online supplemental file).²⁶ We additionally looked for the exposure in different time periods. Thus, the cumulative dose and number of OCS and ICS prescriptions were calculated as a rate per year, identifying prescriptions up to 10 years prior the index date (median patients' record time prior the index date), as well as from the asthma to the index date. The reference category for all analyses was no steroid

exposure. To account for differences in potency of different types of corticosteroids, we converted dosages into prednisolone and beclomethasone equivalent for OCS and ICS, respectively (see online supplemental file)

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the cases and controls. To account for the matched design, we used conditional logistic regression deriving unadjusted and adjusted ORs with 95% CIs assessing the effect of OCS and ICS exposure on the first osteoporosis and FF diagnosis after the asthma date, separately. First, we performed a univariate analysis between the exposure and outcome of interest to establish the unadjusted OR. Our a priori confounders were BMI and smoking status. The next step was to fit the conditional logistic regression model including the exposure of interest and the a priori confounders. Then we added into the model, one at a time, each of the other potential confounding variables, removing this potential confounder before adding the next. We examined how the OR of the exposure of interest changed as we added each potential confounder. If the inclusion of the confounder changed the effect of the exposure of interest by more than 5% then it was an important confounder and should be placed in the fully adjusted model. Missing data for BMI and smoking status were assumed as missing at random and imputed using chained equations. Ten imputations were generated, and the imputed model consisted of all listed confounders, OCS and ICS exposure, and the case-control indicator. Missing data for IMD were assigned a new

Table 3 Association between oral and inhaled corticosteroid exposure in the year prior to the index date and risk of osteoporosis

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted* OR (95%CI)	P value†
	N	%	N	%			
No OCS use (reference)	992	63.4	2607	78.8	1.00	1.00	
OCS prescriptions (n)							<0.0001
1	188	12.0	371	11.1	1.44 (1.19 to 1.77)	1.12 (0.90 to 1.40)	
2-3	123	7.9	189	5.7	1.88 (1.45 to 2.42)	1.34 (1.12 to 1.66)	
4-8	161	10.3	98	3.0	4.74 (3.58 to 6.28)	3.80 (2.81 to 5.13)	
≥9	100	6.4	48	1.5	5.37 (3.69 to 7.82)	4.50 (3.21 to 6.11)	
OCS cumulative dose (mg)							<0.0001
≤500	244	15.6	475	14.4	1.47 (1.23 to 1.77)	1.21 (1.03 to 1.43)	
501–1000	83	5.3	99	3.0	2.44 (1.75 to 3.41)	2.05 (1.57 to 2.68)	
1001–2500	148	9.5	86	2.6	4.77 (3.59 to 6.40)	4.04 (3.12 to 5.12)	
>2500	95	6.1	44	1.3	6.10 (4.15 to 8.98)	4.79 (3.38 to 6.79)	
No ICS use (reference)	569	36.4	1742	52.6	1.00	1.00	
ICS prescriptions (n)							<0.0001
1-6	605	38.7	1053	31.2	1.87 (1.61 to 2.17)	1.35 (1.14 to 1.59)	
7-10	220	14.1	294	8.9	2.49 (2.01 to 3.07)	1.51 (1.20 to 1.92)	
≥11	170	10.9	224	6.8	2.66 (2.08 to 3.39)	1.60 (1.22 to 2.10)	
ICS type							
Beclomethasone	423	27.1	783	23.6	1.75 (1.49 to 2.06)	1.29 (1.08 to 1.54)	.007‡
Budesonide	207	13.2	300	9.1	2.27 (1.82 to 2.83)	1.56 (1.23 to 1.98)	<0.0001‡
Fluticasone	352	22.5	475	14.3	2.44 (2.04 to 2.96)	1.44 (1.18 to 1.77)	<0.0001‡
Ciclesonide	12	0.9	12	0.5	2.55 (1.13 to 5.75)	1.80 (0.76 to 4.27)	.179‡
ICS cumulative dose (mg)§							<0.0001
≤40	209	13.4	433	13.1	1.60 (1.37 to 2.01)	1.18 (0.95 to 1.47)	
41-80	232	14.8	363	10.1	2.07 (1.62 to 2.40)	1.26 (0.98 to 1.60)	
81-120	180	11.5	282	8.5	2.02 (1.74 to 2.72)	1.50 (1.21 to 1.87)	
>120	370	23.7	488	14.7	2.55 (2.01 to 2.97)	1.63 (1.33 to 1.99)	

Percentages have been rounded and so might not total 100.

*Adjusted for smoking, body mass index, social class (ie, Index of Multiple Deprivation), Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions accordingly.

†P values for trend unless otherwise stated. The p values are referred to the adjusted model.

‡P values from the Wald's test.

§Unable to determine cumulative dose in nine individuals.

ICS, inhaled corticosteroid; OCS, oral corticosteroid.

category. The prevalence of those receiving at least one bisphosphonate prescription per steroid prescription category after their initiation the year prior to the index dates was also calculated. Sensitivity analyses were also conducted restricting the samples only to patients with at least one ICS prescription the year prior to the index dates as a stricter definition of asthma as well as restricting the samples only to individuals not in receipt of OCS within the database records examining the relationship between ICS and bone comorbidities eliminating any confounding due to OCS. All analyses were performed in Stata v16.

RESULTS

Characteristics of the study populations

We identified 1564 patients with asthma and osteoporosis, and 3313 control subjects as well as 2131 patients with asthma and fractures and 4421 control subjects from a cohort of 69074 individuals with asthma (tables 1 and 2). The vast majority were women and the mean age was 69.4 (range 26–95) years for osteoporosis and 66.4 (range 18–94) years for fractures. Patients with asthma and both osteoporosis and fracture were more likely to smoke, had more comorbid illness, and were from a lower social class compared with control subjects. The cases were more likely to have a previous diagnosis of fall or fracture and had more prescriptions of bisphosphonates in the previous year than the controls.

Corticosteroids and risk of osteoporosis

A dose–response relationship was observed between the number of prescriptions and cumulative dose the year prior and risk of osteoporosis. Two to three OCS prescriptions were linked with larger odds of osteoporosis, with those receiving more OCS prescriptions (≥9 vs 0 prescriptions; aOR 4.50, 95%CI 3.21 to 6.11) and cumulative doses (≥2500 vs 0mg; aOR 4.79, 95%CI 3.38 to 6.79) being at greater risk (table 3).

ICS exposure was associated with osteoporosis, but the effect was less strong than with OCS. Patients prescribed 11 or more prescriptions were 1.6 times more likely to be diagnosed with osteoporosis than controls (aOR 1.60, 95%CI 1.22 to 2.10), after adjusting for confounders. However, the risk was slightly increased with cumulative doses more than 120mg the year prior to the index date (≥120 vs 0mg; aOR 1.63,

95%CI 1.33 to 1.99). The risk was similar across ICS type, but budesonide had the strongest effect (aOR 1.56, 95%CI 1.23 to 1.98) (table 3).

Corticosteroids and risk of fragility fracture

There was an effect of OCS on risk of FF; however, the effect size was smaller than on osteoporosis. More than nine OCS prescriptions in the previous year had a significant impact on risk (≥9 vs 0 prescriptions; a OR 2.16, 95%CI 1.56 to 3.38), whereas OCS cumulative doses at more than 1000mg led to an increased risk in the previous year, with the risk to be greater at higher doses in comparison to controls (≥2500 vs 0mg; aOR 1.99, 95%CI 1.30 to 3.04) (table 4).

Eleven or more ICS prescriptions were associated with an increased risk of fracture (≥11 vs 0 prescriptions; aOR 1.31, 95%CI 1.02 to 1.68) (table 4). Patients exposed to cumulative doses at more than 120mg in the year prior to the FF were 1.2 times more likely to sustain FF (aOR 1.20, 95%CI 1.08 to 1.42). No significant association between any ICS type and FF was found.

Long-term exposure

The ORs in different period analyses were similar to those found when a 1-year period prior to the index date was used to identify the exposure status (online supplemental tables E2–E5).

Sensitivity analysis

When only patients with at least one ICS prescription before the index dates were included, the risk of both osteoporosis and FF were similar compared with the main analysis (online supplemental tables E6 and E8). After including the patients who never had OCS exposure within the database records, the relationship between ICS, osteoporosis and FF still held (online supplemental tables E7 and E9).

Bisphosphonate use

The prevalence of OCS users receiving at least one bisphosphonate prescription was 31.4% and 21.4% for osteoporosis and FF, respectively (table 5). When ICS users without an OCS prescription in the

Table 4 Association between oral and inhaled corticosteroid exposure in the year prior to the index date and risk of fragility fracture

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted* OR (95%CI)	P value†
	N	%	N	%			
No OCS use (reference)	1663	78.0	3676	83.1	1.00	1.00	
OCS prescriptions (n)							.0002
1	219	10.3	410	9.3	1.23 (1.03 to 1.48)	1.11 (0.91 to 1.34)	
2-3	112	5.3	171	3.9	1.43 (1.10 to 1.85)	1.24 (0.95 to 1.62)	
4-8	85	4.0	123	2.8	1.56 (1.16 to 2.10)	1.31 (1.12 to 1.77)	
≥9	52	2.4	41	1.0	2.70 (1.75 to 4.17)	2.16 (1.56 to 3.38)	
OCS cumulative dose (mg)							0.0001
≤500	279	13.1	507	11.5	1.25 (1.06 to 1.48)	1.11 (0.92 to 1.32)	
501–1000	60	2.8	98	2.2	1.39 (0.98 to 1.96)	1.20 (0.84 to 1.70)	
1001–2500	79	3.7	93	2.1	1.84 (1.33 to 2.55)	1.54 (1.10 to 2.14)	
>2500	50	2.4	47	1.1	2.36 (1.56 to 3.59)	1.99 (1.30 to 3.04)	
No ICS use (reference)	1081	50.7	2527	57.1	1.00	1.00	
ICS prescriptions (n)							.010
1-6	678	31.8	1330	30.1	1.19 (1.05 to 1.35)	1.02 (0.89 to 1.17)	
7-10	219	10.3	340	7.7	1.51 (1.24 to 1.84)	1.24 (1.01 to 1.53)	
≥11	153	7.2	224	5.1	1.66 (1.30 to 2.11)	1.31 (1.02 to 1.68)	
ICS type							
Beclomethasone	510	23.9	984	22.3	1.21 (1.06 to 1.40)	1.10 (0.94 to 1.28)	.213‡
Budesonide	176	8.3	333	7.5	1.29 (1.04 to 1.59)	1.14 (0.90 to 1.44)	.269‡
Fluticasone	341	16.0	548	12.4	1.38 (1.16 to 1.63)	1.04 (0.85 to 1.26)	.679‡
Ciclesonide	16	0.8	74	0.5	2.21 (1.09 to 4.48)	1.75 (0.82 to 3.75)	.145‡
ICS cumulative dose (mg)§							0.021
≤40	257	12.1	560	12.7	1.06 (0.89 to 1.26)	0.94 (0.78 to 1.31)	
41-80	248	11.6	433	9.8	1.35 (1.12 to 1.62)	1.13 (0.93 to 1.63)	
81-120	194	9.1	332	7.5	1.35 (1.10 to 1.65)	1.14 (0.90 to 1.78)	
>120	348	16.3	564	12.8	1.47 (1.25 to 1.74)	1.20 (1.08 to 1.42)	

Percentages have been rounded and so might not total 100.

*Adjusted for smoking, body mass index, social class (ie, Index of Multiple Deprivation), Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions accordingly.

†P values for trend unless otherwise stated. The values are referred to the adjusted model.

‡P values from the Wald's test.

§Unable to determine cumulative dose in 29 individuals.

ICS, inhaled corticosteroid; OCS, oral corticosteroid.

year prior to the index date were included, the percentage of patients receiving at least one bisphosphonate prescription decreased further by around 2%. Only around 50% of patients receiving nine or more OCS prescriptions had at least one bisphosphonate prescription.

DISCUSSION

Our findings provide evidence that both OCS and ICS exposure have deleterious effects on bone health. We found a clear dose–response relationship, with higher cumulative doses and number of OCS and ICS prescriptions being associated with increased odds of osteoporosis and FF. The percentage of patients receiving bisphosphonates after OCS initiation was low.

Our findings are similar to the limited literature. Bloechliger *et al*²⁷ reported a significant dose–response association between first episode of a bone-related condition and cumulative OCS dose in patients with asthma using a nested case-control design, but they did not report the odds for osteoporosis and fractures separately. Similarly, a cross-sectional study found that OCS were associated with an increased OR for osteoporosis (OR 6.55; 95%CI 4.64 to 9.21) and fractures (OR 1.65; 95%CI 1.14 to 2.39) when comparing patients with severe asthma requiring regular OCS treatment with non-asthma controls.¹⁸ Our study adds more details by defining the exposure based on the number of prescriptions and cumulative dose, capturing both the short and long-term users. Cumulative doses more than 1000mg within a year had a significant effect. Price *et al*²⁸ examined the risk of osteoporosis and osteoporotic fractures in patients with asthma exposed to OCS and found similar estimates for cumulative doses. Our data are also in line with a study reporting that the odds of developing bone- and muscle-related complications increased significantly in a dose-dependent manner with OCS use.²⁹ We also found that the number of prescriptions within a year (ie, intermittent use rather than regular) was associated with adverse bone effects, supporting the view that even short courses of OCS are harmful to bone health.⁵

Although the benefits of ICS in asthma are well-documented,³ the detrimental effects of ICS on bones have been less clearly quantified,

with the majority of the limited literature being relevant to the general population and not to asthma. A Canadian study of elderly women failed to detect a high risk of hip fracture (rate ratio 0.92; 95%CI 0.75 to 1.12).³⁰ Suissa *et al*³¹ found no increased risk of fracture at recommended doses of ICS, but they reported a rate ratio of fracture equal to 1.61 (95% CI 1.04 to 2.50) for ≥2000 µg of ICS per day, although this study included only older people (≥65 years) who were already at a higher risk of fractures. Hubbard *et al*³² used CPRD data to reveal a dose–response relationship and increased odds of hip fracture of 1.19 (95% CI 1.10 to 1.28) when adjusting for annual prescriptions of OCS which is similar to the ORs found in our study. Another study, comparing ICS users with non-users, found increased HRs for fracture ranging from 1.13 to 1.51 depending on the fracture site.³³ Our study adds to the literature by providing estimates not only about the risk of osteoporosis, which are lacking, but also of FF, capturing a wide range of severity of asthma, while adjusting for important confounders.

The low percentage of bisphosphonate use after the first OCS prescription in the year prior to the osteoporosis or FF diagnoses is disappointing as this class of drugs is considered the most effective bone protective agent. There is guidance on the prevention of bone loss due to OCS in the general population, suggesting bisphosphonate treatment for adults taking, for more than 3 months, any dose^{34,35} or ≥2.5mg prednisone daily.³⁶ There is no current recommendation for bisphosphonate therapy among ICS users. We found that only a minor percentage of ICS users at high risk had at least one bisphosphonate prescription after the first ICS prescription in the year prior to the osteoporosis or FF date.

Current guidelines on asthma do not cover the management of bone comorbidities in detail. Although the British Thoracic Society/Scottish Intercollegiate Guidelines Network and the GINA guidelines on asthma management cover specific comorbidities including osteoporosis, no specific bone protection guidance is given^{2,3} and the asthma guideline from the National Institute for Health and Care Excellence (NICE) does not mention osteoporosis at all.³⁷ Our results suggest that risk and prevention of osteoporosis and FF should be addressed explicitly in future guideline updates.

Table 5 Prevalence of patients using at least one bisphosphonate prescription after the oral and inhaled corticosteroid initiation in the year prior to the osteoporosis and fragility fracture diagnosis

Type of exposure	Osteoporosis			Fragility fractures		
	Patients with at least one BP prescription	Patients per corticosteroid category	Prevalence	Patients with at least one BP prescription	Patients per corticosteroid category	Prevalence
	N	N	%	N	N	%
OCS prescriptions (n)						
Overall	401	1275	31.4	259	1208	21.4
1	108	559	19.3	92	629	14.6
2-3	99	309	31.7	50	283	17.6
4-8	119	259	45.9	72	208	35.5
≥9	75	148	50.6	45	93	48.4
ICS prescriptions (n)						
Overall	868	2566	33.8	573	2944	19.4
1-6	532	1658	32.0	348	2008	17.3
7-10	191	514	37.1	120	559	21.4
≥11	145	394	36.8	105	377	27.8
ICS prescriptions* (n)						
Overall	467	1579	29.5	314	1685	18.6
1-6	314	1100	28.5	203	1434	14.2
7-10	90	280	32.1	63	348	18.1
≥11	63	199	31.6	48	217	22.1

ICS users without an OCS prescription the year prior to the index date.
BP, bisphosphonate; ICS, inhaled corticosteroid; OCS, oral corticosteroid.

The main strengths of our study are the large study size and use of linked data. By using linked data, we have been able to provide more complete estimates of osteoporosis and fractures incidence, capturing not only those recorded in primary care as vertebral fractures or osteoporosis often do not come to clinical attention in primary care, and people might not be aware of these conditions³⁸ before a hospitalisation. Our study reports separately the risk stratifying data by dose, number of prescriptions, and type of OCS and ICS providing pragmatic guidance to clinicians. The dose-response relationship between ICS, osteoporosis and fractures held, even after excluding each individual with a previous OCS exposure within the database records. The population-based setting means the findings are generalisable to the wider population.

This study has some limitations. Diagnostic misclassification may occur, as we were reliant on general practitioners recording these conditions. However, these diagnoses have been previously validated in the database, demonstrating a positive predictive value of around 90%.^{39,40} Because of the nature of our data, we may have included some non-fragility fractures; however, we acted properly to minimise as much as possible this bias. The dose-response relationship may need to include number of years on OCS or ICS; however, the patients' medical records do not go back indefinitely. Patients may have been using a drug prescribed before the examined index periods; however, this would bias the results towards the null hypothesis. Inhalers can be difficult to use correctly, and adherence is unlikely to be perfect, leading to lesser intake of actual dose underestimating the relationship between a prescribed ICS dose and bone health. Our exposure was defined based on corticosteroid prescriptions and not on actual compliance.

CONCLUSIONS

In summary, both OCS and ICS are associated with an increased risk of osteoporosis and FF in people with asthma. The use of OCS and ICS should be kept to the minimum necessary to treat symptoms and should be stepped down if symptoms and exacerbations are well managed. Bisphosphonate comedication should be considered according to guidelines for bone protection.

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Contributors CVC had full access to all the study data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: CVC, DES, TMM; acquisition of data: CVC; analysis of data: CVC; interpretation of data: CVC, DES, TMM; drafting the article: CVC; revision for important intellectual content and approval of the version to be published: CVC, DES, TMM.

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Teste de avaliação de DPOC para avaliação dos sintomas de COVID-19

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RESUMO

Existem evidências que demonstram os sintomas contínuos da COVID-19. Contudo, atualmente, não existem resultados consensuais para a avaliação destes sintomas. Este estudo examinou a utilização do teste de avaliação (TAC) para doença pulmonar obstrutiva crônica (DPOC) em doentes em recuperação de COVID-19. 131 doentes admitidos com COVID-19 foram acompanhados por contacto telefónico para avaliação dos sintomas. A pontuação mediana (IQR) do TAC foi de 10 (5-16). As categorias de tosse, fleuma e aperto no peito encontravam-se dentro dos limites para pessoas saudáveis, mas registaram-se indícios de falta de ar, perda de energia, atividade e distúrbios do sono. A TAC é uma ferramenta útil para avaliar os sintomas de recuperação da COVID-19.

INTRODUCTION

Symptoms due to the SARS-CoV-2 (COVID-19) are varied but the chief respiratory symptoms are cough, sputum and breathlessness.¹ It is not clear how long these specific symptoms persist after the initial acute event but it is becoming clear that some patients will have complex rehabilitation needs.^{1,2} Due to the novel nature of the disease, there are no outcome measures specifically designed to assess patients following COVID-19. The chronic obstructive pulmonary disease (COPD) assessment test (CAT) is an eight-item questionnaire designed to assess common COPD symptoms but has been used in many respiratory diseases and is widely used within respiratory medicine and pulmonary rehabilitation.³ It uses an eight-point differential item response scale to assess: cough, sputum, chest tightness, breathlessness, activity limitation, confidence leaving the home, sleep and energy. These domains have significant overlap with the commonly reported symptoms for patients experiencing COVID-19. The CAT has been used in healthy subjects in whom the mean score was 6.9 (SD 6.2),³ with 83% of healthy volunteers screened having a CAT score of <10.4 These normative data allow us to assess patients with COVID-19 in the absence of a previous CAT score. The aim of this study was to assess the use of the CAT total and item scores in patients recovering from COVID-19 in order to assess symptom-based needs.

METHODS

This was an observational cohort study of patients discharged from hospital following an admission of COVID-19, either by positive swab or clinical diagnosis. All patients admitted with COVID-19 to the University Hospitals of Leicester were eligible for this study. Patients were followed up by a phone consultation after discharge to assess symptoms and rehabilitation needs. Participants were excluded if their primary cause for admission was not COVID-19 or its related symptoms. They were recruited and completed the CAT over the phone. Participants also completed the Functional Assessment of Chronic Illness Therapy (FACIT)⁵ and Hospital Anxiety and a Depression Scale (HADS)⁶ questionnaire, alongside baseline demographic information and self-reported physical activity (categorised as no exercise experience, exercised previously but not currently or currently undertakes exercise, or reports 30min of activity per day for 5 days). Information was collected about their admission including hospital bed days and number of days ventilated.

Data were analysed using SPSS V.25. Associations between length of stay, ventilation status and ques-

tionnaires and CAT total and item scores were tested using Spearman's rank order correlation.

RESULTS

One hundred and thirty-one patients were recruited, 30.5% had a pre-existing respiratory condition, mainly asthma (15.3%) and COPD (9.9%). The mean (SD) time to telephone call post discharge was 32 (18) days. Participants were predominantly men (58.8%) with a mean (SD) age of 60 (14) years. The average length of stay was 10 (12) days with 21 (16%) patients requiring ventilation (invasive n=18 or non-invasively n=3). One-third of which, (34%) had a pre-existing respiratory condition and the mean (SD) number of comorbidities was 1.9 (1.5), ranging from 0 to 7.

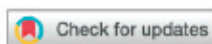
Median (IQR) CAT total and item scores are shown in table 1 and figure 1. In the whole population, 52% had CAT total scores ≥ 10 . Of the patients with no pre-existing lung disease 42% had score ≥ 10 , and in the patients with preexisting lung disease this proportion was 75%.

There were no statistically significant correlations with the CAT with length of stay ($r=-0.07$, $p=0.41$), number of days ventilated ($r=0.10$, $p=0.69$) or FACIT ($r=0.05$, $p=0.57$). There were statistically significant moderate correlations with the HADS anxiety ($r=0.51$, $p<0.01$) and depression ($r=0.57$, $p<0.01$) scores and self-reported physical activity ($r=0.26$, $p<0.01$). There were no correlations between CAT score and time between discharge and telephone call ($r=-0.14$, $p=0.13$) (figure 2) or time between admission and follow-up call ($r=0.07$, $p=0.46$). The mean (SD) FACIT Score was 27.7 (13.9) with n=58 (54%) demonstrating 'severe fatigue', but there were no statistically significant differences in those with/without severe fatigue in length of stay, number of days ventilated, CAT total or item scores, or HADS.

DISCUSSION

These results demonstrate a high CAT total score for patients following an admission of COVID-19. Symptoms relating to the airways (cough, phlegm and chest tightness) scored close to previously reported healthy persons of a similar age⁴; however, those with a pre-existing respiratory disease had higher phlegm scores. In contrast, breathlessness, activity limitation, confidence to leave the home, sleep and energy were worse, even in patients with no previous diagnosed lung disease. Confidence leaving the house appears to be a concern, but this should be framed in the context of lockdown and social distancing measures, so it is difficult to ascribe causality to this item score. There was a relationship between CAT and anxiety and depression and it is possible that a higher burden of symptoms can lead to anxiety and depression but also anxiety and depression may lead to increased severity of symptoms. Unlike other critically ill patients, patients with COVID-19 are exposed to mass media reporting of their condition and the impact this may have on symptom reporting or anxiety and depression is unknown.

Patients with pre-existing lung disease were more likely to have CAT scores ≥ 10 than those without due to more breathlessness, activity limitation and sleep disturbance, but loss of energy was similar in the two groups. This similarity is unlikely to be due to a 'floor effect'; since the scoring range for each item is 0–5 and scores are ≈ 2.6 for both groups. We conclude that poor energy is principally due to the post-COVID-19 state.



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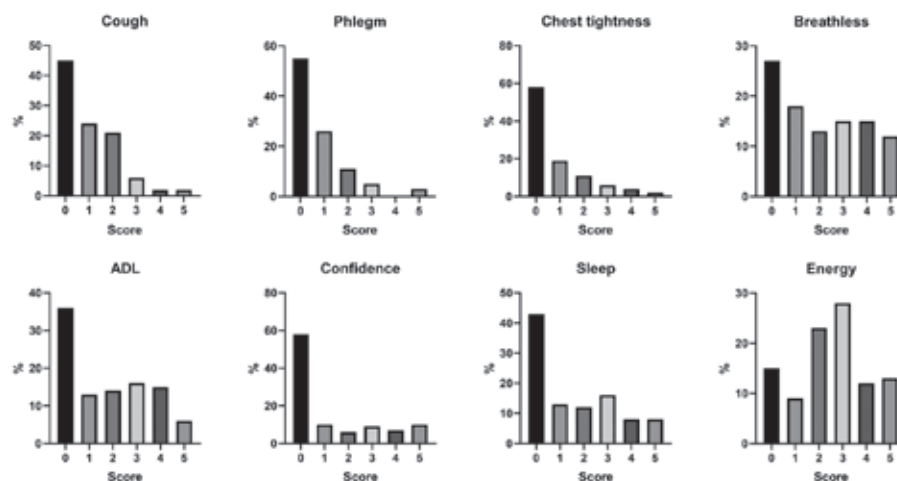


Figure 1 Percentage of participants scoring 0–5 per domain of the COPD assessment test. ADL, activities of daily living; COPD, chronic obstructive pulmonary disease.

Table 1 Mean (SD) for all patients and split by presence or absence of pre-existing respiratory disease

Type of exposure	All n=131	No pre-existing lung disease n=91	Pre-existing lung disease n=40	P value	Non-COPD persons* n=481
CAT total	10 (5–16)	9 (5–14)	13 (8.75–18.75)	<0.01	6.9 (6.2)
Cough	1 (0–2)	1 (0–2)	1 (0–2)	0.42	1.3 (1.1)
Phlegm	0 (0–1)	0 (0–1)	1 (0–2)	0.05	0.8 (1.1)
Chest tightness	0 (0–1)	0 (0–1)	0 (0–2)	0.96	0.6 (1.0)
Breathlessness	2 (0–4)	2 (0–3)	3 (1–4)	0.02	1.0 (1.3)
Activity limitation	2 (0–3)	1 (0–3)	2 (0–4)	0.14	0.6 (1.1)
Confidence to leave home	0 (0–3)	0 (0–3)	0 (0–2)	0.82	0.2 (0.8)
Sleep	1 (0–3)	1 (0–3)	2 (0–4)	0.05	0.9 (1.2)
Energy	3 (2–4)	3 (1–4)	3 (2–3)	0.70	1.4 (1.2)

Non-COPD persons—data from Raghavan *et al*⁴ presented as mean (SD).

CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease.

The time to follow-up call from discharge varied between patients, with a large SD and while we may have expected a trend to reducing symptoms over time, the length of follow-up did not affect the results. This suggests either limited/slow natural recovery or potentially higher initial CAT scores if patients were followed up earlier. The time to first contact was affected by staffing and high numbers of discharge early on. Follow-up would ideally be within 1 week of discharge. The study sample demonstrated a higher presence of respiratory conditions and a younger group than previously reported. This sample was representative of those who were admitted to the University Hospitals of Leicester, which is a specialist respiratory centre and may explain the increased presence of pre-existing respiratory disease. As this was an observational cross-sectional analysis, the change in CAT score over time is yet to be explored. Additionally, the CAT was administered over the phone; however, it has previously been demonstrated to have high validity when conducted over the phone, which is comparable to face to face administration.⁷ This study explored the use of the CAT in previously hospitalised patients and its exploration in patients with COVID-19 (symptoms or diagnosis) in the community is important, given that their experiences may be different; however, it is quick and easy to administer and could add value to assessments in primary care and the community.

The results of this study demonstrate higher reported symptoms for four out of eight items on the CAT and that total scores ≥ 10 were seen

in over half of patients including those without previous lung disease. Global Initiative for Chronic Obstructive Lung Disease⁸ has recommended that CAT scores ≥ 10 in patients with COPD should be the threshold for maintenance treatment in COPD. While the CAT score can assess needs for rehabilitation, there is no defined threshold for patients whom might benefit from intervention post-COVID-19. It is important that a recovery programme addresses all aspects of the condition including anxiety and depression. There is an established minimal clinical important difference of two points in patients with COPD⁹; however, the application of this to a COVID-19 needs to be assessed due to social influences on symptom perception and expectations of treatment benefit in this condition. While the CAT can be used to guide treatment but further research is needed to identify impact of interventions.

The CAT can provide insight into the severity of symptom burden for patients following a hospitalisation for COVID-19 and could be considered to assess ongoing symptoms following COVID-19.

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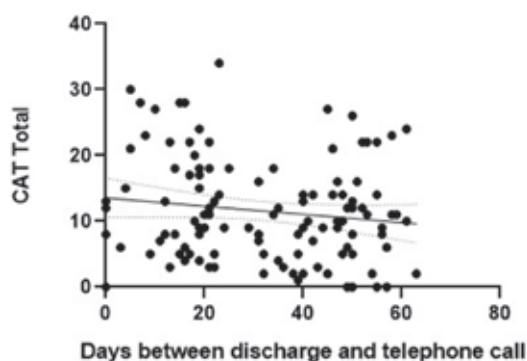


Figure 2 COPD assessment test (CAT) total score and time to phone call from discharge. COPD chronic obstructive pulmonary disease.

'COVID de longo prazo': um estudo transversal dos sintomas persistentes, biomarcadores e anomalias imagiológicas após a hospitalização por COVID-19

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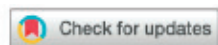
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RESUMO

Um elevado número de pessoas está a receber alta hospitalar na sequência da COVID-19 sem ser submetida a uma avaliação da recuperação. Em 384 doentes (idade média de 59,9 anos; 62% do sexo masculino), no seguimento de uma mediana de 54 dias após a alta hospitalar, 53% referiu falta de ar persistente, 34% tosse e 69% fadiga. 14,6% apresentou depressão. Entre os que receberam alta hospitalar com biomarcadores elevados, 30,1% apresentou d-dímeros elevados e 9,5% proteína C-reativa elevada. 38% das radiografias de tórax permaneceram anormais, com 9% em deterioração. O acompanhamento sistemático após hospitalização com COVID-19 identifica a trajetória da carga dos sintomas físicos e psicológicos, a recuperação dos biomarcadores sanguíneos e imagiológicos que poderiam ser utilizados para informar a necessidade de reabilitação e/ou de mais investigações.

INTRODUCTION

Large numbers of people are being discharged from hospital following COVID-19 without systematic assessment of their recovery and need for rehabilitation or further investigation to detect complications. Initial reports are emerging of significant ongoing symptom burden¹ termed 'Long-COVID', and of changes in lung function² and imaging.³

METHOD

We rapidly established a post-COVID follow-up service across three large London hospitals, collecting data to identify unmet health needs and to identify people requiring additional rehabilitation and/or investigation for complications. In brief, we aimed to follow up all SARS-CoV-2 positive COVID-19 admissions by phone or in-person four-to-six weeks after discharge. Key symptoms were graded as absent, or present on an 11-point (0-10) scale in which a higher score was more severe. We invited people with abnormal blood tests or imaging at discharge to repeat these. Imaging was classified using British Society of Thoracic Imaging criteria.⁴ Full details of our follow-up procedures and protocol are included as an online supplemental appendix.

RESULTS

This report summarises the clinical assessment of 384 patients reviewed a median of 54 (IQR 47-59) days following hospital discharge with COVID-19. Three hundred eighty-four patients represent 34% of the total number of patients with COVID-19 discharged during this period (online supplemental figure 1). Of the 479 patients we attempted to contact, we were able to complete the call in 395 (82%) and of these only 11 (2.8%) declined to participate. Data for 79 of the 95 patients in who we were unable to complete the follow-up demonstrate similar age, sex, ethnicity and comorbidity to those we were able to follow-up.

The characteristics of the 384 participating subjects, and a summary of their COVID-19 admission are reported in table 1. In brief, the population had a mean age of 59.9 years and were predominantly male. Only 34% had no reported comorbidity. Forty-three per cent were from a black, Asian or minority ethnic background. Eight per cent of the cohort was obese.

The median length of hospital stay was 6.5 (4-10.75) days and 14.5% required admission to intensive care.

Patients graded their overall recovery health as a median (IQR) 90 (75-100)% compared with 100% best health. Recovery towards usual health was lower in those with comorbidity (as listed in table 1) compared with those without: 85 (70-100)% versus 92.5 (80-100)%, $p=0.007$. Persistence of symptoms at follow-up, by level of acute respiratory support, is reported in table 1. Follow-up symptoms were least prevalent in those treated with oxygen alone. Further detail on the assessment of physical symptoms at follow-up is reported in online supplemental table 1, including symptom intensity in relation to maximum, and the proportions reporting the trajectory of symptoms to be improving, unchanged or deteriorating. For all symptoms at follow-up, there was a statistically significant improvement from maximum intensity to follow-up ($p<0.0001$). In those with persistent breathlessness, patients assessed earlier post discharge tended to have higher breathlessness scores (figure 1) suggesting a trend to improvement over time. The trajectory for cough, fatigue and sleep quality is illustrated as online supplemental figures 2-4. 14.6% of participants had a PHQ2 score of greater than 3 indicating significant depression.

The results of blood investigations at admission, the last time point prior to discharge and follow-up, are reported in table 2. Overall, despite significant abnormalities at discharge, blood test results had returned to normal levels in the majority of patients at follow-up. Of those with abnormal discharge results and who attended for further blood tests, 7.3% of 247 patients had persisting lymphopaenia, 30.1% of 229 patients had elevated d-dimer and 9.5% of 190 patients had elevated C reactive protein (CRP). The d-dimer value was decreasing over time (online supplemental figure 5).

At presentation, 333/384 (87%) patients had a chest radiograph performed. Of these, 49 (15%) were normal, 188 (56%) were typical of COVID-19 and 96 (29%) were indeterminate for or unlikely to represent COVID-19. Of the radiographs classified as typical for COVID-19, 4 did not have a severity grading, 49/188 (26%) were reported as mild, 78/188 (41%) as moderate and 57/188 (30%) as severe. Of the 244/384 (66%) patients that had follow-up radiographs, 151 (62%) radiographs were normal, 66 (27%) demonstrated significant improvement, 4 (2%) were unchanged and 23 (9%) showed significant deterioration. Of the patients with radiographs that demonstrated worsening at follow-up, 2/23 (9%) had been normal at presentation, 10/23 (43%) had been typical for COVID-19 and 11/23 (48%) had been indeterminate for or unlikely to represent COVID-19. 14.8% of follow-up patients were deemed to require further assessment with CT chest imaging, pulmonary function tests, other investigations or a face-to-face review.

DISCUSSION

Our data show that while symptom burden in subjects recovering from hospital admission with COVID-19 had generally improved at early follow-up, 53% reported persistent breathlessness, 34% persistent cough and 69% persistent fatigue. Fifteen per cent were depressed. Of people who attended for repeat imaging and blood tests because investigations on discharge had

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Table 1 Baseline characteristics, features of the acute COVID illness and symptom persistence at follow-up following hospital discharge**Subject characteristics**

Age (n=384, years)	59.9±16.1
Sex M:F (n=384, %)	62:38
Ethnicity (n=368)	British Caucasian 38.8% (n=139/368) Other Caucasian 17.1% (n=63/368) British Asian 6.5% (n=24/368) Other Asian 10.3% (n=38/368) Black British 6.8% (n=25/368) Other black 7.6% (n=28/368) Other ethnicity 13.9% (n=51/368)
Comorbidities	Hypertension 41.9% (n=155/370) Diabetes mellitus 27.2% (n=101/371) Asthma and/or COPD 17.5% (n=65/371) Chronic kidney disease 11.0% (n=41/372) Ischaemic heart disease 9.7% (n=36/371)
Smoking: current/ever/never (n=373, %)	2.7/23.3/60.9
Covid illness	
Duration of symptoms prior to admission (n=372, days)	7 (4–10)
Level of care (n=367)	Oxygen alone: 59.1% (n=217) ICU: 14.5% (n=54) Intubation: 7.1% (n=47)
Length of stay (n=384, days)	6.5 (4–10.75)
Clinical Frailty Score on Admission (n=384)	2 (2–3.75)
Symptom persistence* (n=276)	
Breathlessness	54.8/63.3/57.7
Oxygen alone/CPAP/IV (%)	
Cough	32.2/36.7/46.2
Oxygen alone/CPAP/IV (%)	
Fatigue	67.3/73.3/76.9
Oxygen alone/CPAP/IV (%)	
Poor sleep quality	61.1/93.3/76.9
Oxygen alone/CPAP/IV (%)	

Data reported as mean (±SD), median (IQR) or % as appropriate.

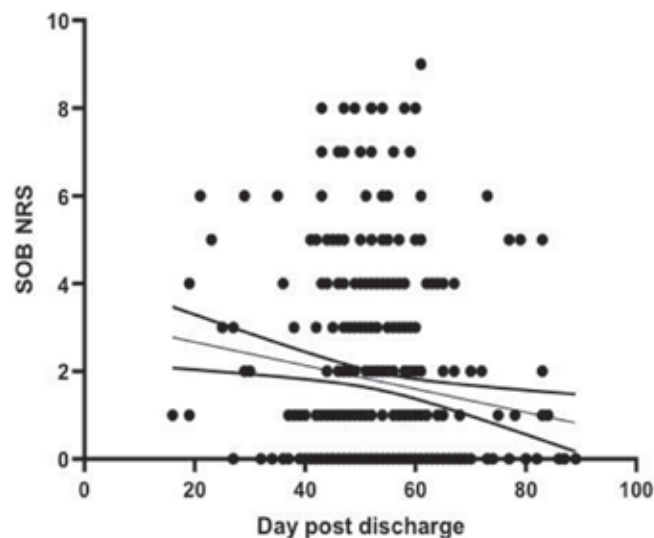
*Persistence defined as symptom score ≥1.

IV, invasive ventilation.

been abnormal, 9% had a deteriorating chest radiograph appearances at follow-up, and 30.1% and 9.5% had persistently elevated d-dimer and CRP concentration respectively. COVID-19 is associated with increased risk of thrombosis⁵ but the significance of the persistent elevation in d-dimer is unclear. Deteriorating chest radiograph appearances raise the possibility of developing lung fibrosis. These data are compatible with studies reporting longer term abnormalities in SARS survivors,⁶ and initial data emerging from smaller COVID-19 cohorts.¹⁷

There are strengths and weaknesses to this analysis. We only included those who tested positive for SARS-CoV-2, and patients requiring prolonged ICU and inpatient stay may be underrepresented in this early analysis. Comparing against maximal symptoms risks recall bias and other symptoms such as chest pain may also be important. Not all participants were willing to take part in the review, or attend for investigations, potentially introducing selection bias. We cannot determine if these features are unique to COVID-19 or similar to those following admission for other critical respiratory illness.

To conclude, we provide the first report of physical and psychological symptom burden, blood markers and chest imaging trajectory following discharge for a hospitalised episode of COVID-19. We have

**Figure 1** Patient reported breathlessness (0–10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90% CI. A higher score represents more severe breathlessness.

identified persisting symptoms and radiological abnormalities in a significant proportion of subjects. These data may assist with the identification of people outside expected recovery trajectories who could benefit from additional rehabilitation and/or further investigation to detect post-COVID complications. Identifying which patients have persistent dyspnoea due to complications rather than deconditioning alone is an important question for future research.

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Table 2 Blood investigations at admission to hospital, discharge and follow-up

	N	Admission	Predischarge	Follow-up
WCC (×10 ⁹ /L)	337	6.99 (5.07–9.29)	6.85 (5.44–8.71)	6.49 (5.6–7.8)
Platelets (×10 ⁹ /L)	337	218 (169–276.5)	334 (243–445)	247 (210–294)
Lymphocytes (×10 ⁹ /L)	337	0.95 (0.69–1.3)	1.23 (0.92–1.69)	1.94 (1.44–2.52)
D-dimer ng/mL	176	785 (510–1486)	878.5 (547.5–2522.5)	384 (242–665)
Ferritin µg/L	197	861 (430–1671)	795 (440–1458)	169 (86–271)
Creatinine µmol/L	335	84 (68–106)	71 (59.7–89)	80 (68–91)
ALT (iu/L)	288	36 (25–58.5)	46 (30–71.3)	26 (19–39)
AST (iu/L)	146	45 (31.8–68.5)	44 (27–67)	24 (20–30)
Glucose mmol/L	187	6.6 (5.5–7.9)	6.9 (5.2–8.5)	5.9 (5.2–7.2)
CRP mg/L	332	76 (36–157)	38 (16–78)	1 (1–4)

Data expressed as median (IQR).

ALT, alanine transaminase; AST, aspartate transaminase; CRP, C reactive protein; WCC, white cell count.

Identificação de doentes em risco de complicações após alta hospitalar relacionadas com a infeção por COVID-19

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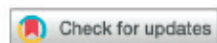
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RESUMO

A infeção por SARS-CoV-2 é uma doença multissistémica com sequelas após a alta hospitalar. Reportámos dados de seguimento referentes aos primeiros 200 doentes internados num hospital do Reino Unido com uma recuperação lenta da doença. 4 semanas após a alta hospitalar, 321/957 sobreviventes (34%) apresentavam sintomas persistentes. Desenvolveu-se um protocolo estruturado de avaliação clínica ambulatória e os resultados dos primeiros 200 doentes observados entre 4-6 semanas após a alta são aqui apresentados. Em 80/200 (40%), identificámos uma causa cardiorespiratória para a falta de ar no seguimento, incluindo anomalia parenquimatosa persistente (64 doentes), embolia pulmonar (quatro doentes) e complicações cardíacas (oito doentes). Estas descobertas ocorreram tanto em doentes internados em unidade de cuidados intensivos (UCI) como em doentes tratados em enfermaria, embora os doentes que necessitavam de internamento em UCI fossem mais suscetíveis de apresentar uma causa cardiorespiratória significativa pela sua falta de ar, com um rácio de risco de 2,8 (95% IC 1,5 a 5,1).

BACKGROUND

On 11 March 2020, WHO declared SARS-CoV-2 or COVID-19 a global pandemic. As of late December 2020, 2 149 551 cases had been recorded in the UK.¹ The long-term outcome for these patients is unknown. However, recent studies indicate potential long-term complications ranging from disturbance of taste/smell,² cough,³ fatigue and dyspnoea²⁻⁵ to more pronounced cardiac,⁶ respiratory^{3 4 7} and cognitive dysfunction.^{3 7}

METHOD

As the early Guy's and St Thomas' Hospital patients diagnosed with COVID-19 were being discharged, a post-COVID clinic was established to address the unmet needs of those with persistent symptoms. All patients attending the Hospital with either a positive PCR for COVID-19 or a negative PCR but a clinical/radiological diagnosis were telephoned 4 weeks after discharge. Those with persistent symptoms and those who had required intensive care unit (ICU) admission were invited for review. Those reporting a return to baseline were offered a chest radiograph at 12 weeks, consistent with national guidance.⁸

Patients attending the clinic were evaluated⁴⁻⁶ weeks post-discharge by Respiratory or Infectious Disease Specialists. Further details of the follow-up pathway are found in figure 1. History and physical examination were undertaken; data collected on baseline characteristics and function; chest radiograph and blood tests performed; and health status questionnaires completed. Patients completed a 6 min walk test (6MWT) where physically able.

Further assessment was based on physiological impairment and patient-reported symptoms. Available investigations included: dual energy CT or high-resolution CT, ventilation/perfusion scanning, spirometry with gas transfer (limited due to the aerosol-generating nature of the procedure), echocardiography and ECG. Onward referral to other specialist teams for early assessment was effected.

Data collected was analysed using SPSS V.27 (IBM). Variables are expressed as mean±SD for parametric data or median ±IQR for nonparametric data. ICU versus non-ICU values are compared either by independent samples t-test for parametric variables or by mann-whitney U test for non-parametric variables. Risk ratios are calculated using a X² analysis.

RESULTS

By the end of May 2020, 1272 patients had been diagnosed with COVID-19 of whom: 1239 (97%) had PCR-confirmed disease; 241 (19%) patients had died; 74 (6%) remained as inpatients. Of the remaining 957 patients: 122 (13%) were uncontactable, 61 (6%) declined any further follow-up, 139 (15%) were considered unsuitable to attend clinic because they were housebound due to frailty or because they were unwell with unrelated conditions; 314 (33%) had returned to functional baseline. Three hundred and twenty-one (34%) patients reported persistent symptoms and were invited for clinical review. We report data from the first 200 patients with a PCR confirmed diagnosis who were seen due to persistent symptoms.

The mean age was 54.8±15.0, 61.5% were male and the majority were overweight (mean body mass index 28.8±6.1). Further characteristics are described in table 1.

Of the 200 seen, 179 had received inpatient care, the remaining 21 patients been discharged directly from the emergency department. The majority had not been critically unwell and only 55 (27.5%) patients had ever received mechanical ventilation. Other features of their admission are highlighted in table 2.

During evaluation (table 3), patients reported their Medical Research Council (MRC) dyspnoea score (graded 1–5) post-illness and retrospectively graded their baseline score pre-illness. A persistent deterioration of two or more MRC points was observed in 36 (18%) patients. Of the 170 patients that underwent 6MWT, 34 (20%) had an oxygen desaturation of 4% or more. Of those that went on to complete lung function tests (n=59), 16 (27%) had a predicted forced vital capacity of 80% or less and 26 (44%) had a transfer factor for carbon monoxide of 70% or less. Screening for anxiety and depression, using standardised tools, identified similar prevalence to that seen in general medical inpatients.⁹

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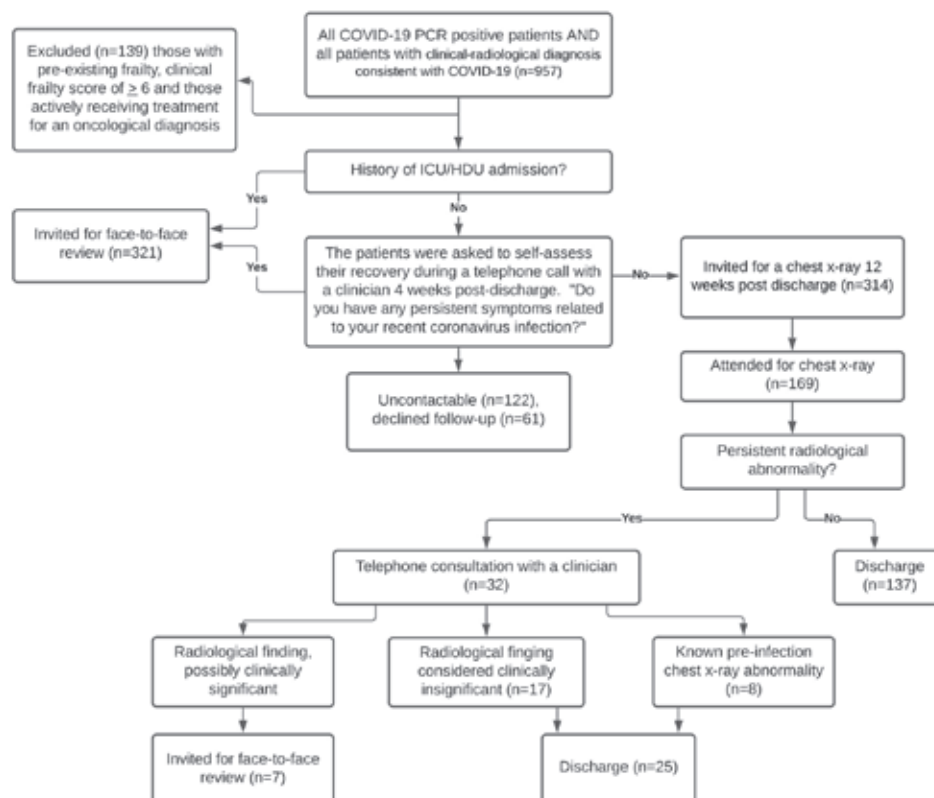


Figure 1 Post-discharge follow-up pathway outcomes. ICU, intensive care unit; HDU, high dependency unit.

The dominant finding in those seen was persistent interstitial change in 64 (32%) patients on CT. Other respiratory findings included 4 (2%) patients with a previously unidentified pulmonary embolus, lung infarcts (n=2), *Klebsiella pneumonia* (n=1) and *Pneumocystis jirovecii pneumonia* (n=1). Either a previously undiagnosed or deterioration of existing cardiac cause for ongoing symptoms was found in eight patients (4%): pericarditis, persistent sinus tachycardia, hypertrophic cardiomyopathy and inferior regional wall motion abnormality, an atrial septal defect with new reversal of shunt, pulmonary hypertension, left ventricular hypertrophy and worsening of pre-existing heart failure.

Asymptomatic patients were followed up as per national guidance with chest radiograph at 12 weeks, 169/314 (54%) attended. Of these, 137 (81%) patients had a film reported as normal by a radiologist. The remaining patients were reviewed by telephone, 8 (2.5%) had known preinfection abnormalities to their chest X-ray but 24 (14%) had residual parenchymal change. Seventeen patients (10%) had no symptoms or change in function and so no further follow-up was arranged. For 7/169 (4%) cases, possible persistent issues

were identified and these patients were offered face-to-face clinical assessment.

DISCUSSION

With the COVID-19 global pandemic yet to peak, these early results indicate likely long-term morbidity in a significant number of patients. Of those seen, 119/200 (60%) had persistent subjective symptoms despite no radiological or physiological abnormality being identified and these patients with 'post-COVID-19 syndrome' are likely to create a considerable healthcare management dilemma. However, 40% of those seen did have a significant finding. A limitation of our work is that only symptomatic patients were physically reviewed, and while only 4% of these patients went on to have significant findings requiring further follow-up, we advise screening for persistent symptoms in all patients in the weeks after discharge to ensure complications are identified. In addition, given these patients were admitted early in the pandemic, our non-ICU cohort had relatively mild disease, with only 50% requiring oxygen therapy. These findings suggest that more thorough follow-up of patients is indicated than is currently recommended under the BTS guidance,⁸ and support the more robust approach advised in by the recently published National Institute for Health and Care Excellence guidelines.¹⁰ The outcome of this cohort of early patients highlights the current limitations of our knowledge of COVID-19 recovery. Planned studies, such as the UK-based post-hospitalisation COVID-19 study (PHOSPCOVID), will further elucidate the clinical trajectory and improve understanding of differences in patient outcomes.

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Contributors AD and AW conceived of the idea. JLL was responsible for data entry and data management. KM, TM and JH were responsible for performing the computations. KM verified the analytical methods. JH wrote the manuscript with KM, AD, AW and BM supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Table 1 Baseline characteristics

	(n=200)	ICU (n=77)	Non-ICU (n=123)
Age (years) (mean±SD)	54.8±15.0	53.1±14.0	55.7±15.4
Sex (% male)	61.5	66.2	58.5
BMI (kg/m ²) (mean±SD)	28.8±6.1	30.8±14.8	29.1±6.1
Current smokers (%)	30 (15.0)	13 (9.8)	12 (15.7)
Comorbidities (%)			
Obesity	72 (36.0)	37 (48.1)	35 (28.5)
Diabetes	55 (27.5)	21 (27.3)	34 (27.6)
Hypertension	72 (36.0)	32 (41.6)	40 (32.5)
COPD	4 (2.0)	1 (1.3)	3 (2.4)
Cardiovascular risk factors (%) hypertension, diabetes, smoking and obesity			
0	69 (34.5)	17 (22.1)	52 (42.3)
≥1	131 (65.5)	31 (40.3)	32 (26.0)
≥2	68 (34.0)	17 (22.1)	42 (19.5)
≥3	27 (13.5)	11 (14.3)	14 (11.4)
4	2 (1.0)	1 (1.3)	1 (0.8)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Table 2 Admission characteristics

	(n=200)	ICU (n=77)	Non-ICU (n=123)	ICU versus non-ICU
Inpatient (%)	89.5			
Length of stay (days) (median $\pm$ IQR)	9 $\pm$ 15	20 $\pm$ 20	4 $\pm$ 7	p<0.001
Oxygen therapy (%)	139 (69.5)	77 (100.0)	62 (50.4)	
Maximum required FIO ₂ (%)	n (%)			
21	61 (30.5%)	0 (0.0)	61 (49.6)	
24–36	53 (26.5%)	5 (6.5)	48 (39.0)	
40%–60%	35 (17.5%)	21 (27.3)	14 (11.4)	
>60%	51 (25.5%)	51 (66.2)	0 (0.0)	
Invasive mechanical ventilation (%)	55 (27.5)	55 (71.4)	na	
Inpatient systemic steroid treatment, oral or intravenous (%)	29 (14.5)	21 (27.3)	8 (6.5)	
Peak d-dimer (0.00–0.55 mg/L)	3.5 $\pm$ 10.6	19.9 $\pm$ 25.9	3.1 $\pm$ 10.5	p<0.001
Peak ferritin (30–400 μ g/L) (median $\pm$ IQR)	1360 $\pm$ 1450	2492 $\pm$ 1518	775 $\pm$ 1206	p<0.001
Nadir lymphocyte (1.2–3.5 $\times$ 10 ⁹ /L) (median $\pm$ IQR)	0.70 $\pm$ 0.30	0.6 $\pm$ 0.3	0.9 $\pm$ 0.5	p<0.001
Peak C reactive protein (0–4 mg/L) (median $\pm$ IQR)	241.0 $\pm$ 235	304.5 $\pm$ 211	102.0 $\pm$ 162	p<0.001

FIO₂, fractional inspired oxygen; ICU, intensive care unit.**Table 3** Structured assessment clinic

	(n=200)	ICU (n=77)	Non-ICU (n=123)	ICU versus non-ICU
MRC (median $\pm$ IQR)	2 $\pm$ 1	3 $\pm$ 1	2 $\pm$ 1	p=0.026
Delta MRC (median $\pm$ IQR)	1 $\pm$ 1	1 $\pm$ 1	1 $\pm$ 1	p=0.04
6MWT (n=170)				
Distance (m)	342 $\pm$ 169	342 $\pm$ 305	429 $\pm$ 306	p=0.181
% predicted (median $\pm$ IQR)	70.4 $\pm$ 42.0	63.9 $\pm$ 54.5	70.4 $\pm$ 40.8	
Resting SpO ₂ (%) (median $\pm$ IQR)	96.0 $\pm$ 2.0	96.0 $\pm$ 2.0	96.0 $\pm$ 2.3	p=0.996
Nadir SpO ₂ (%) (median $\pm$ IQR)	94 $\pm$ 4	94 $\pm$ 4	94 $\pm$ 4	p=0.858
>4% desaturation	34	12	22	p=0.693
Max HR (median $\pm$ IQR)	111 $\pm$ 17	108 $\pm$ 20	115 $\pm$ 16	p=0.310
D-dimer (0.00–0.55 mg/L) (median $\pm$ IQR)	0.48 $\pm$ 1.00	0.99 $\pm$ 1.00	0.46 $\pm$ 1.00	p=0.126
Ferritin (30–400 μ g/L) (median $\pm$ IQR)	164 $\pm$ 234	186 $\pm$ 234	145 $\pm$ 216	p=0.340
Lymphocyte (1.2–3.5 $\times$ 10 ⁹ /L) (median $\pm$ IQR)	1.9 $\pm$ 1.0	2.1 $\pm$ 1.0	1.8 $\pm$ 0.9	p=0.001
C reactive protein (0–4 mg/L) (median $\pm$ IQR)	6.2 $\pm$ 2.0	6.5 $\pm$ 3.0	2.0 $\pm$ 3.0	p=0.597
Questionnaires				
PHQ9 (median $\pm$ IQR)	3.0 $\pm$ 11.0	7.0 $\pm$ 12	8.0 $\pm$ 11.3	p=0.621
PHQ9 $\geq$ 10 (%)	32 (16%)	11 (14.3)	21 (17.1)	
GAD7 (median $\pm$ IQR)	4.0 $\pm$ 9.5	8.0 $\pm$ 11.0	3.0 $\pm$ 6.0	p=0.168
GAD7 $\geq$ 10 (%)	22 (11%)	11 (14.3)	11 (8.9)	
STOPBANG (median $\pm$ IQR)	3.0 $\pm$ 2.0	3.0 $\pm$ 1.0	2.5 $\pm$ 1.8	p=0.682
STOPBANG $\geq$ 4 (%)	36 (18.0)	12 (15.6)	22 (17.0)	
				RR (95% CI)
Cardiorespiratory cause of breathlessness	81 (40.5)	43 (55.8)	38 (30.9)	2.8 (1.5 to 5.1)
Persistent parenchymal change (%)	64 (32.0)	35 (45.5)	29 (23.6)	2.7 (1.4 to 4.9)
PE (%)	4 (2.0)	1 (1.3)	3 (2.4)	0.5 (0.1 to 5.1)
Other respiratory (%)	5 (2.5)	4 (5.1)	1 (0.8)	6.7 (0.7 to 60.1)
Cardiac (%)	8 (4.0)	2 (2.6)	6 (4.9)	0.7 (0.2 to 2.6)

GAD7, generalised anxiety disorder questionnaire 7; HR, heart rate; ICU, intensive care unit; 6MWT, 6 min walk test; PHQ9, patient health questionnaire 9; RR, risk ratio; SpO₂, oxygen saturations; STOPBANG, snoring, tiredness, observed apnoeas, high blood pressure, BMI, age, neck circumference and male gender questionnaire.

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Hesitação na vacinação em países de rendimentos médios e baixos: potenciais implicações para a resposta à COVID-19

Sunil Bhopal,^{1,2} Maryke Nielsen^{3,4,5}

Nesta fase da pandemia da COVID-19, as crianças são relativamente poupadas aos efeitos diretos do vírus SARS-CoV-2, mas o seu papel na transmissão é pouco compreendido. As conclusões sobre estas questões exigem prudência, uma vez que a natureza da pandemia e do vírus é mutável. As organizações mundiais de saúde e os governos nacionais estão a colocar esperanças num regresso a uma quase normalidade no desenvolvimento de uma vacina segura e eficaz que possa ser rapidamente fabricada e fornecida em todo o mundo para uma utilização em larga escala em tempo recorde. Atualmente, existem mais de 100 candidatos a vacinas deste tipo com estudos de fase 1, 2 e 3 em curso. Os adultos em risco elevado de COVID-19 podem optar, na sua esmagadora maioria, por receber uma vacina, mas continua por esclarecer se uma campanha de vacinação dirigida exclusivamente a adultos será suficiente para interromper a transmissão.

Alguns especialistas estimam que, no mínimo, será necessária uma imunização de 60% da população.¹ Este número aumenta se o R_0 aumentar. Particularmente nos países de rendimentos médios e baixos (PRMB) com uma elevada proporção de jovens e programas de vacinação de adultos não muito bem implantados, a vacinação infantil generalizada poderá também vir a ser necessária. Isto leva-nos a considerar a provável aceitabilidade de uma nova vacinação COVID-19 para crianças, que são - nesta fase da pandemia - na sua maioria pouco afetadas pela COVID-19. A boa notícia é que as vacinas são amplamente aceites nos PRMB. De acordo com os resultados do *Wellcome Global Monitor* de 2018, um inquérito a 140000 indivíduos em 140 países sobre as opiniões públicas em relação à saúde e à ciência, 94% e 90% dos participantes no Sul da Ásia e na África Oriental, respetivamente, descreveu a vacinação como eficaz. Do mesmo modo, 95% e 92% dos participantes no Sul da Ásia e na África Oriental consideraram as vacinas como seguras.² Em comparação com a Europa Ocidental, apenas 59% dos participantes consideraram as vacinas como seguras. É de salientar que esta perceção de segurança foi mais elevada nos países de rendimentos baixos, de rendimentos médios inferiores e de rendimentos médios superiores, onde os inquiridos reportaram níveis mais elevados de confiança em cientistas, médicos e enfermeiros. O Grupo de Trabalho SAGE da OMS sobre Hesitação Vacinal descreve a hesitação numa continuidade entre a aceitação total e a recusa total e reconhece que a hesitação pode ser em relação a uma ou várias vacinas.³

A investigação com recurso à Escala de Hesitação de Vacinas do SAGE (Grupo Consultivo Estratégico de Peritos em Imunização) da OMS

sugeriu que, mesmo entre uma população pró-vacinas de 2265 inquiridos do Bangladesh, China, Etiópia, Guatemala e Índia (95% concordaram que “as vacinas infantis são importantes para a saúde do meu filho”), mais de 50% concordaram ou foram neutras no que diz respeito à questão “as novas vacinas comportam mais riscos do que as vacinas mais antigas”.⁴ A investigação realizada em países de rendimentos altos sugere que os indivíduos estão naturalmente dispostos a correr mais riscos em relação a novas vacinas para crianças quando os benefícios diretos são superiores,⁵ mas esta pode ser uma situação diferente para a vacina COVID-19 para crianças. Como em todas as infeções, existem crianças de maior risco, mas mesmo o impacto da infeção diretamente sobre as populações infantis vulneráveis nos PRMB, muitas vezes com elevada carga de subnutrição e crianças portadoras ou expostas ao VIH, ainda não foi completamente descrito. É necessário um envolvimento forte e contínuo da comunidade local e nacional e uma criação de confiança para aumentar tanto a aceitação como a procura por todas as vacinas.

É importante que, na urgência de se usar novas vacinas, se tenha o cuidado de assegurar que os programas implementados mantêm a confiança e continuam a proteger as crianças, tendo em conta a confiança dos pais e a tendência para a complacência e a importância da conveniência (o “modelo dos três C”) na redução do comportamento hesitante relativamente às vacinas.³ Esta situação não é inédita. Em 2017, descobriu-se que uma nova vacina contra a dengue (Dengvaxia) apresentava riscos para indivíduos nunca expostos à dengue. Nas Filipinas, esta notícia foi recebida com indignação política e social, com aumentos drásticos das preocupações manifestadas relativamente à eficácia, segurança, importância percebida e mesmo compatibilidade com crenças religiosas documentadas pelo *Vaccine Confidence Project*.⁶

Os investigadores, governos e agências mundiais devem atuar com especial cuidado na avaliação das vacinas candidatas para o SARS-CoV-2 nos PRMB, assegurando uma comunicação eficaz para criar confiança e evitar a hesitação na vacinação. A eficácia da vacina é muitas vezes altamente variável entre cenários de recursos elevados e escassos. A dinâmica da transmissão do SARS-CoV-2 em países com populações predominantemente jovens, o que é verdade para muitos PRMB, é largamente desconhecida. Para ser aceite, é fundamental que qualquer vacina que se pretenda utilizar em PRMB se comprove ser segura e eficaz nos contextos em que se pretende utilizar. As recentes observações de investigadores franceses de que as vacinas candidatas deveriam ser testadas primeiro em África foram recebidas com indignação e acusações de racismo. Os cientistas posteriormente pediram desculpa, mas os danos para a confiança na investigação da COVID-19 no continente poderão ser difíceis de reparar.

Uma atenção inadequada à comunicação e a perceção de um secretismo, particularmente no contexto de um medo exacerbado de uma epidemia, podem ser desastrosos. Em 2015, dois ensaios de vacinas contra o Ébola no Gana foram

suspensos e subsequentemente abandonados, como resposta às acusações dos meios de comunicação social de que os investigadores estavam a infetar os participantes com o vírus Ébola.⁷ É imperativo que, na pressa justificável de avaliar uma nova vacina para a COVID-19, a confiança nos programas de vacinação existentes não seja posta em causa através de uma comunicação científica pouco eficiente, falta de envolvimento público ou confiança insuficiente de que os governos atuam no melhor interesse da saúde e segurança públicas e com base em provas científicas sólidas. Talvez o maior risco de hesitação da vacina nos próximos meses e anos seja causado por fatores relacionados com a própria resposta à COVID-19. Os programas de vacinação foram restringidos em mais de 20 países como resposta a rigorosas medidas de distanciamento social, mesmo em países com surtos de sarampo ativos.

A pandemia alterou significativamente o comportamento dos pais em matéria de saúde. Uma sondagem recente mundial da OMS revelou que 73% dos países registaram uma redução na procura de imunização, sendo superior nos países da região africana da OMS (89%). Quase metade dos inquiridos sugeriu que o público tem preocupações relativamente ao risco de exposição à COVID-19 ao participar na vacinação (www.who.int/immunization/monitoring_surveillance/immunizationand-covid-19/). É necessário um trabalho urgente para tornar os centros de vacinação e o transporte da vacina da COVID-19 seguros, juntamente com o envio de mensagens de saúde pública interligadas para fazer face a estes receios. Celebramos o progresso científico, o que significa que o desenvolvimento de uma vacina para este novo vírus é mesmo uma consideração. Também podemos estar um pouco mais tranquilos pelo facto de que a hesitação de vacinas nos PRMB continua a ser, de um modo geral, reduzida. No entanto, esta hesitação reduzida é frágil e não deve ser tomada como certa. As comunidades e as famílias devem ser incluídas na tomada de decisões para assegurar que populações inteiras se movimentem em conjunto e de forma solidária.

Pequenos erros, incluindo problemas de segurança, assim como medidas de distanciamento social necessárias, podem ter consequências graves e involuntárias em termos de imunização para uma eventual vacina para a COVID-19 e para vacinações de rotina. Impõe-se cuidado e cautela para protegermos as nossas crianças.

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Impacto da pandemia da COVID-19 na saúde infantil global: declaração conjunta do International Child Health Group e do Royal College of Paediatrics and Child Health

International Child Health Group, Royal College of Paediatrics & Child Health

- ▶ As mães, recém-nascidos e crianças - especialmente nos países mais pobres - sofrem impactos indiretos significativos na saúde e nos cuidados como consequência da COVID-19, com efeitos adversos potenciais a longo prazo.
- ▶ Governos, beneméritos, agências internacionais e organizações da sociedade civil empenhados em confrontar a COVID-19 têm de monitorizar de forma colaborativa e transparente e informar publicamente sobre os efeitos da resposta pandémica nas famílias e crianças.
- ▶ Os investimentos globais na recuperação da COVID-19 devem dar prioridade a uma nova era de investimento em sistemas de saúde sólidos que apoiem um modelo de saúde centrado na família e programas de saúde infantil. Apesar dos efeitos diretos nas crianças do vírus COVID-19 serem raros até ao momento, os efeitos indiretos da pandemia COVID-19 a nível mundial podem ser catastróficos para as crianças, com um considerável excesso de mortalidade e sofrimento.^{1,2}

Espera-se que muitas das principais causas de saúde precária e mortalidade infantil aumentem este ano, como consequência da pandemia e da resposta. Ao mesmo tempo, verifica-se uma diminuição da capacidade de resposta dos governos, sistemas de saúde, desenvolvimento e organizações humanitárias face à saúde infantil. O acesso à vacina já está a ser comprometido devido à resposta da COVID-19 e às restrições de transporte, com grande impacto nos países de rendimentos baixos.³ As atividades de vacinação foram adiadas ou suspensas em pelo menos 27 países para evitar a propagação da COVID-19, apesar de vários terem epidemias de sarampo em curso.⁴ Mais de 100 milhões de crianças podem ficar sem vacinação contra o sarampo este ano⁵ e podem seguir-se outros surtos evitáveis.

Os modelos sugerem que cada morte por COVID-19 evitada pela suspensão da vacinação de rotina no sentido de reduzir a transmissão poderá provocar muitas mais mortes.⁶ Também se prevê

que as mortes por malária infantil dupliquem este ano⁷ devido à diminuição da prevenção e do tratamento. O Programa Alimentar Mundial prevê uma duplicação da malnutrição, afetando desproporcionadamente as crianças.⁸ Os serviços de saúde materna e infantil, muitos dos quais já sofriam de um contexto de subinvestimento, resiliência limitada e procura precária, estão agora severamente comprometidos em muitos cenários de recursos reduzidos devido a encerramentos, ao receio de frequentar instalações de saúde e à falta de equipamento de proteção pessoal.⁹

Nos próximos 6 meses, poderão ocorrer mais de um milhão de mortes de crianças.¹⁰ A saúde mental e a segurança das crianças também estão em risco devido à perturbação das condições socioeconómicas e ambientais necessárias para uma infância saudável e ao exacerbamento da violência e abuso familiares e baseados no género.¹¹ As dificuldades das crianças que vivem na pobreza são agravadas, sendo uma consequência do desemprego e da insegurança nos rendimentos.^{12,13} As raparigas, nomeadamente, podem abandonar a educação à medida que as famílias reentram na pobreza e a posição das crianças migrantes e refugiadas tornou-se mais precária.¹⁴ O fardo das consequências indiretas da pandemia recairá desproporcionadamente sobre as crianças, mas estamos alarmados com a pouca atenção que as suas necessidades estão a receber. Os profissionais de saúde infantil devem defender que as necessidades das crianças se tornem mais visíveis e que os direitos de todas as crianças à proteção, sobrevivência, participação e desenvolvimento sejam defendidos no âmbito de ações globais e nacionais. Devemos assegurar que o impacto da pandemia na saúde e nas experiências das crianças seja visível nos dados e na tomada de decisões, reforçando a vigilância dos efeitos indiretos e transmitindo esta informação ao público em geral.

Enquanto a atenção se centra nas intervenções dirigidas para a COVID-19, com ênfase na segurança sanitária global, os governos, as organizações internacionais e o setor privado também devem dar prioridade à continuação e apoio dos programas de saúde infantil ao longo

de toda esta pandemia. As crianças não podem ser ignoradas.

Correction notice This paper has been updated since it was published online. One of the collaborators' names has been amended.

Twitter International Child Health Group @intchildhealth

Collaborators International Child Health Group: Neal Russell; Natalie Prevatt; Andrew Clarke; Sunil Bhopal; Delan Devakumar; Amaran Uthayakumar-Cumarasamy; Maryke Nielsen; Paula de Sousa; Beth Stinchcombe. Royal College of Paediatrics and Child Health: Sebastian Taylor; Susan Broster; Russell Viner.

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COVID-19 pediátrica crítica: apresentações variadas, mas prognósticos positivos

Relatórios internacionais sobre a pandemia da COVID-19 têm descrito o seu impacto relativo sobre as crianças, tanto na frequência de casos¹ como na gravidade da doença.²⁻⁴ A principal apresentação descrita em crianças é a síndrome inflamatória pediátrica multissistêmica temporariamente associada ao SARS-CoV-2 (PIMS-TS) - muitas destas crianças não apresentam evidências de doença viral positiva em PCR e, portanto, podem representar um fenómeno pós-infeccioso.⁵ Descrevemos a nossa experiência numa unidade de cuidados intensivos pediátricos (UCIP) de crianças que testaram positivo para SARS-CoV-2 nas primeiras 10 semanas da pandemia no Reino Unido, excluindo as que cumpriram os critérios PIMS-TS, uma vez que estes foram descritos noutros locais. Foi admitido nas nossas unidades de cuidados intensivos

(UCI) um total de 313 crianças entre 26 de março de 2020 e 31 de maio de 2020.

96 crianças apresentaram suspeitas de COVID-19, das quais 24 (25%) testaram positivo por transcrição reversa (RT-PCR) no aspirado nasofaríngeo à admissão. Treze crianças apresentaram um fenótipo PIMS-TS. No presente artigo, descrevemos as características e o curso das 11 crianças restantes. As características demográficas e de apresentação são apresentadas no quadro 1. As comorbilidades estiveram presentes em nove das onze crianças. Quatro (36%) crianças eram de origem negra, asiática ou minoria étnica. As características clínicas são apresentadas no quadro 2. Foram levantados marcadores inflamatórios, mas o intervalo de valores máximos durante a admissão foi muito variável. Quatro crianças apresentaram doenças respiratórias que preencheram os critérios PALICC 2015 (*paediatric acute lung injury consensus conference*) para a síndrome de desconforto respiratório agudo pediátrico. A gestão da insuficiência respiratória hipoxêmica incluiu a ventilação em posição prona (n=4) e vasodilatadores pulmonares inalados (n=3).

Duas crianças foram escaladas para oscilação de alta frequência devido a hipoxia refratária na ventilação convencional. A duração mediana da ventilação foi de 13 dias (IQR 10-15,5 dias). As restantes sete crianças necessitaram de admissão em UCI por razões diferentes de insuficiência respiratória. Três crianças apresentaram o estatuto de epilepsia (duas com distúrbios convulsivos conhecidos e uma com um traumatismo craniano adquirido). Todas testaram negativo para SARS-CoV-2 na análise do líquido cefalorraquidiano. Três crianças apresentaram novos diagnósticos significativos (doença cardíaca congénita, leucemia e diabetes mellitus) que teriam exigido a admissão em UCI, independentemente do seu estado SARS-CoV-2. A outra criança estava a realizar quimioterapia para uma malignidade e fazia ventilação de longo prazo, mas não exigiu um aumento significativo dos seus parâmetros ventilatórios. Duas crianças da corte encontravam-se imunocomprometidas.

Entre outras terapias, cinco (45%) crianças receberam medicação vasoativa. Nenhuma recebeu terapia de substituição renal ou oxigenação por membrana extracorporeal. Cinco crianças (45%) receberam

Table 1 Presentation characteristics of children presenting to PICU with a PCR-positive diagnosis of SARS-CoV-2 infection. Children who presented with a paediatric inflammatory multisystem syndrome were excluded from this description

Characteristics	Patients (n=11)
Median age, years (IQR)	5 (0.4–11.1)
Male, n (%)	9 (81)
Ethnicity: Black, Asian and minority ethnic, n (%)	4 (36)
PIM3 predicted mortality, n (%)	
<1%	5 (42)
1%–5%	4 (36)
5%–15%	1 (9)
15%–30%	0
>30%	1 (9)
Coexisting disorder, n (%)	
Weight above 91st centile	3 (27)
Cancer	1 (9)
Pre-existing respiratory disease*	2 (18)
Prematurity	2 (18)
Congenital heart disease	1 (9)
Median duration of symptoms before admission, no of days (IQR)	2 (1.5–3)
Primary presenting symptoms, n (%)	
Cough	6 (55)
Apnoea	3 (27)
Fever	10 (90)
Gastrointestinal (abdominal pain/vomiting/diarrhoea)	6 (55)
Seizures†	3 (27)
Microbiology	
SARS-CoV-2 RT-PCR positive on nasopharyngeal aspirate	11 (100)
RSV or influenza RT-PCR positive on nasopharyngeal aspirate	0
Sputum cultures positive for other organisms	2 (10)‡
Blood culture positive for other organisms	
Chest radiography findings, n (%)	0
No new parenchymal changes	3 (64)
Parenchymal changes including acute on chronic changes	8 (36)

*Pre-existing respiratory disorder included chronic lung disease and non-cystic fibrosis bronchiectasis.

†Two of the children presented had previously defined epilepsy.

‡Equivocal growth of *Staphylococcus aureus* and *Candida albicans*.

PICU, paediatric intensive care unit; PIM3, paediatric index of mortality version 3; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2 Summary of clinical characteristics and interventions for children with a PCR-positive diagnosis of SARS-CoV-2 infection. Children who presented with a paediatric inflammatory multisystem syndrome were excluded from this description

Blood markers	Median measurement (range)
Maximum leucocyte count ($\times 10^9/L$)	15.4 (6.01–24.75)
Lymphocyte count ($\times 10^9/L$)	1.15 (0–2.94)
Maximum ferritin ($\mu g/L$)	898 (264–1991)
Maximum LDH (units/L)	1594 (802–4264)
Maximum D-dimer ($\mu g/L$)	1655 (162–6742)
Maximum CRP (mg/L)	158 (27–449)
Maximum temperature during ICU admission ($^{\circ}C$), median (IQR)	39.5 (38.4–40)
OSI, median (IQR)	
Day 1	5.2 (4.1–7.0)
Day 2	6.6 (4.3–7.6)
Day 3	5.1 (3.6–6.74)
ICU therapies, n (%)	
Invasive mechanical ventilation	9 (81)
Prone position	4 (36)
Neuromuscular blockade	5 (46)
Inhaled pulmonary vasodilators*	4 (36)
High-frequency oscillation ventilation	2 (11)
Renal replacement therapy	0
ECMO	0
Vasoactive drugs	5 (46)
Anticoagulation, n (%)	
Therapeutic dose	3 (27)
Prophylactic dose	5 (46)
Antiviral medication, n (%)	
Remdesivir	5 (46)
Outcomes	
Survival to ICU discharge	11
Survival to hospital discharge	11
Median length of ICU stay (IQR), days	10 (3.2–13.0)

Entire ranges presented for maximum or minimum blood parameters rather than IQRs.

*Inhaled nitric oxide or inhaled prostacyclin.

†Leucocyte and lymphocyte counts include results from two children with oncological diagnoses.

‡OSI data exclude data from two children not ventilated and one child prior to correction of cyanotic congenital heart disease.

CRP, C reactive protein; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LDH, lactate dehydrogenase; OSI, oxygen saturation index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

uso compassivo de remdesivir após revisão ética. Seis crianças (55%) receberam anticoagulação profilática como parte de uma alteração das nossas práticas habituais. As duas crianças desenvolveram trombose associada a cateter na ausência de profilaxia e necessitaram de terapêutica anticoagulante. Todas as crianças sobreviveram à alta da UCIP. Apesar de as crianças se poderem apresentar na UCIP com um padrão de doença semelhante à COVID-19 de adultos, esta situação é rara e três quartos das crianças apresentaram fatores de risco para infecções respiratórias. Por coincidência, verificou-se que um número considerável de crianças estava infetada com SARS-CoV-2. Embora não se possa excluir uma relação causal entre algumas apresentações e a infeção por SARS-CoV-2, estes casos terão implicações nas medidas de controlo de infeções hospitalares em crianças com doenças críticas durante a pandemia.

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A COVID-19 não constitui um fator de pieira viral e asma clinicamente significativos

No início do ano letivo, existe um afluxo de crianças com ataques de pieira viral e asma que se apresentam na urgência pediátrica. No Reino Unido, a pandemia de COVID-19 resultou em extensos encerramentos de escolas e na implementação de medidas de distanciamento social nas escolas. O nosso objetivo foi determinar até que ponto a SARS-CoV-2 foi identificada em crianças admitidas em hospital com pieira viral e/ou asma no início do ano letivo de 2020 e comparar as tendências de apresentação com os anos anteriores. Leicester foi a primeira cidade no Reino Unido a ter um confinamento geográfico específico imposto pelo facto de as taxas de infeção por SARS-CoV-2 por dimensão da população estarem acima da média.¹

Comparámos o período de 4 anos, 2017-2020, e extraímos dados sobre apresentações e admissões na nossa unidade de urgência pediátrica terciária (antes do COVID-19, as visitas consistiam em 60000 por ano) durante as primeiras 4 semanas do ano letivo (quadro 1). Uma admissão foi definida como uma decisão de admissão num hospital ou cama de internamento de curta duração. De acordo com a orientação do governo, apenas as crianças admitidas em hospital são submetidas a exame de esfregaço para diagnóstico de SARS-CoV-2. A avaliação foi registada na comissão de auditoria e melhoramento

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Table 1 Breakdown of presentations (viral wheeze and asthma combined) per year

Time frame	Presentations	Admitted (%)	Intensive care admissions
2017 (23/8–20/9)	187	123 (65.7)	1
2018 (30/8–27/9)	290	187 (64.5)	3
2019 (29/8–26/9)	229	139 (60.7)	2
2020 (24/8–21/9)	237	133 (56.1)	1

hospitalar (10786). Em 2020, não se verificaram amostras positivas de SARs-CoV-2 em crianças admitidas com ataques de pieira viral ou asma durante o início do ano letivo. Os nossos dados indicariam que, na nossa localidade, o SARS-CoV-2 não está a exercer qualquer influência no pico anual de pieira viral e nas admissões por asma. Existe o risco de erro de interpretação de tipo 2 devido ao tamanho relativamente pequeno da amostra, mas a ausência completa de resultados positivos leva-nos a crer que tal seja improvável.

Anteriormente, o nosso departamento já demonstrou uma taxa global muito reduzida de SARS-CoV-2 em crianças admitidas, que apoiaria estas conclusões.² A nossa conclusão também pressupõe um fenótipo de gravidade da asma semelhante a cada ano, que acreditamos ser uma pressuposição razoável devido ao número muito semelhante de apresentações e resultados ao longo dos anos.

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Controle a asma^{1,2}

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LABA (ICS)

INALHAÇÃO

1 VEZ AO DIA

Revinty
furoato de fluticasona + vilanterol ELLIPTA

ELE CONTROLA

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

1) Woodcock A *et al.* Lancet 2017; 390:2247–2255. 2) Bateman ED *et al.* Thorax 2014; 69:312–319. 3) GINA. Global strategy for asthma management and prevention, 2020. Available at: <https://ginasthma.org/-gina-reports/> (Acedido: março 2021). 4) VestboJ *et al.* Lancet 2016;387:1817-1826. ICS: Corticosteroide inalado; LABA: Agonista β_2 de longa duração de ação.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM • NOME DO MEDICAMENTO Revinty Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Revinty Ellipta 92/22 mcg: Cada inalação disponibiliza uma dose administrada de 92 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 100 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifrenatato). Revinty Ellipta 184/22 mcg: Cada inalação disponibiliza uma dose administrada de 184 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 200 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifrenatato). Cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose **INDICAÇÕES TERAPÉUTICAS** Asma: Revinty Ellipta 92/22 mcg e 184/22 mcg está indicado para o tratamento regular da asma em adultos e adolescentes com idade ≥ 12 anos em que a utilização de um medicamento contendo uma associação (agonista β_2 , de ação prolongada e corticosteroides para inalação) é adequada: doentes que não estão adequadamente controlados com corticosteroides para inalação e com agonistas β_2 , de curta duração de ação 'conforme o necessário'; doentes que estão já adequadamente controlados com corticosteroides para inalação e com agonistas β_2 , de ação prolongada. **DPOC:** Revinty Ellipta 92/22 mcg está indicado para o tratamento sintomático de adultos com DPOC com um FEV₁ previsível normal $<70\%$ (após o broncodilatador) com antecedentes de exacerbação apesar da terapêutica regular com um broncodilatador. **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Asma (92/22 mcg e 184/22 mcg) **Adultos e adolescentes ≥ 12 anos** Deve considerar-se uma dose inicial de uma inalação de 92/22 mcg uma vez por dia para adultos e adolescentes ≥ 12 anos que requeiram uma dose baixa a média de corticosteroides para inalação em associação com um agonista β_2 , de ação prolongada. Se os doentes não estiverem corretamente controlados com 92/22 mcg, a dose pode ser aumentada para 184/22 mcg. Os doentes devem ser regularmente reavaliados. A dose deve ser titulada para a dose mais baixa com a qual é mantido um controlo efetivo dos sintomas. Revinty Ellipta 184/22 mcg deve ser considerado para adultos e adolescentes ≥ 12 anos que requeiram uma dose mais elevada de corticosteroides para inalação em associação com um agonista β_2 , de ação prolongada. Os doentes normalmente verificam uma melhoria na função pulmonar 15 minutos após a inalação. É necessário o uso diário regular para manter o controlo dos sintomas de asma e o uso deve ser continuado mesmo quando esta é assintomática. Se os sintomas surgirem no período entre as doses, deve ser utilizado um agonista β_2 , de curta duração de ação, por inalação, para o alívio imediato. A dose máxima recomendada é 184/22 mcg 1x/dia. **Crianças <12 anos** A segurança e a eficácia ainda não foram estabelecidas na indicação para a asma. **DPOC (92/22 mcg)** **Adultos ≥ 18 anos** Uma inalação 1x/dia. Os doentes normalmente verificam uma melhoria na função pulmonar 16-17 minutos após a inalação. **População pediátrica** Não existe utilização relevante na população pediátrica para a indicação de DPOC. **Populações especiais** **Idosos (> 65 anos)** e **Compromisso renal** Não é necessário ajustar a posologia. **Compromisso hepático** Estudos revelaram um aumento na exposição sistémica ao FF. Devem tomar-se precauções na definição da posologia em doentes com compromisso hepático que possam estar em risco mais elevado de reações adversas sistémicas associadas a corticosteroides. Para os doentes com compromisso hepático moderado ou grave a dose máxima é de 92/22 mcg. **Modo de administração** Via inalatória. Deve ser administrado à mesma hora do dia, todos os dias. Se uma dose for omitida, deve tomar-se a próxima dose à hora habitual no dia seguinte. Após inalação, os doentes devem enxaguar a boca com água sem a engolir. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram cefaleia e nasofaringite. Com a exceção de pneumonia e fraturas, o perfil de segurança foi semelhante em doentes com asma e DPOC. Durante os estudos clínicos, pneumonia e fraturas foram mais frequentemente observadas em doentes com DPOC. **Infeções e infestações** Frequentes Pneumonia, infeção do trato respiratório superior, bronquite, gripe, candidíase da boca e da garganta **Doenças do sistema imunitário** Raras Reações de hipersensibilidade incluindo anafilaxia, angioedema, erupção cutânea e urticária **Doenças do metabolismo e da nutrição** Pouco Frequentes Hiperglicémia **Perturbações do foro psiquiátrico** Raras Ansiedade **Doenças do sistema nervoso** Muito frequentes Cefaleia Raras Tremor **Afeções oculares** Pouco frequentes Visão turva **Doenças cardíacas** Pouco frequentes Extra-sístoles Raras Palpitações, taquicardia **Doenças respiratórias, torácicas e do mediastino** Muito frequentes Nasofaringite Frequentes Dor orofaríngea, sinusite, faringite, rinite, tosse, disfonia Raras Broncospasmo paradoxal **Doenças gastrointestinais** Frequentes Dor abdominal **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia, dor de costas, fraturas, espasmos musculares **Perturbações gerais e alterações no local de administração** Frequentes Pirexia. **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** fevereiro 2021. **APRESENTAÇÃO:** Revinty Ellipta 92 mcg+22 mcg, 30 doses; Revinty Ellipta 184 mcg+22 mcg, 30 doses. **Regime de comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. **Medicamento Sujeito a Receita Médica.** Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial- Portela & C^a, S.A., -A Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. As Marcas Registradas são propriedade ou licenças das empresas do grupo GSK. (C) 2021 empresas do grupo GSK ou sob licença. DMGMA_PT210310

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