

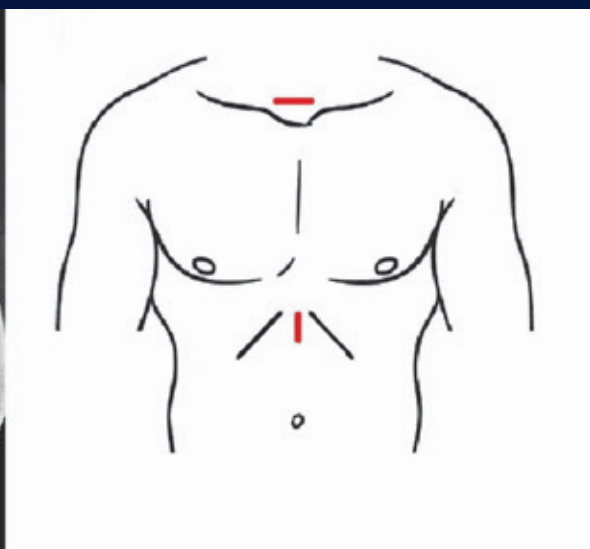
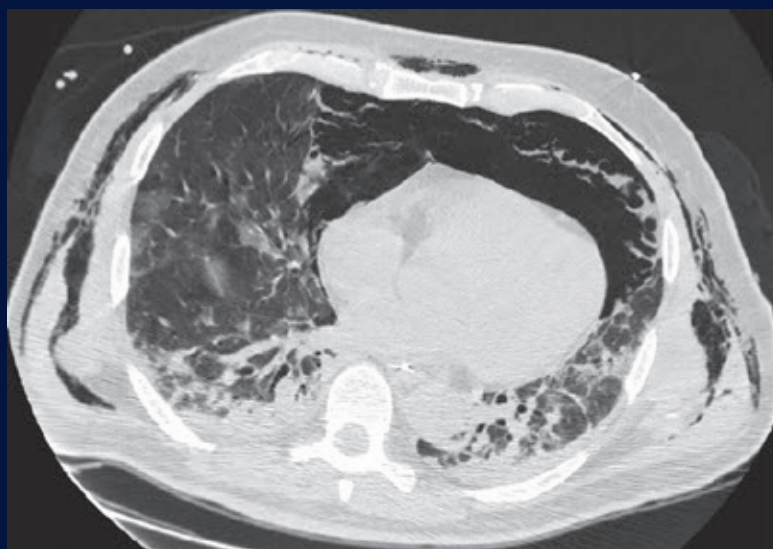
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ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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ARCHIVES OF
DISEASE IN
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UMA TRIPLA
ASSOCIAÇÃO.
UMA ÚNICA TOMA³.
Um novo fôlego na DPOC.



LAMA | LABA | ICS



1 INALAÇÃO



1 VEZ AO DIA



1 DISPOSITIVO

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

Referências: 1. Van der Palen J et al. NPJ Prim Care Respir Med 2016 26:16079 2. Lipson DA et al. N Engl J Med 2018 378:1671-1680 3. RCM Elebrato Ellipta, setembro 2020
DPOC: Doença pulmonar obstrutiva crônica; ICS: Corticosteroide inalado; LABA: Agonista β2 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/submissaoar> e para o departamento médico da GlaxoSmithKline para lis.nucleo-farmacovigilancia@gsk.com.

NOME DO MEDICAMENTO Elebrato Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 92 microgramas de furoato de fluticasona, 65 microgramas de brometo de umeclidínio equivalente a 55 microgramas de umeclidínio e 22 microgramas de vilanterol (como trifenatato). Isto corresponde a um recipiente unidose de 100 microgramas de furoato de fluticasona, 74,2 microgramas de brometo de umeclidínio equivalente a 62,5 microgramas de umeclidínio e 25 microgramas de vilanterol (como trifenatato). Excipiente com efeito conhecido: cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada. **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose. **INDICAÇÕES TERAPÉUTICAS** Tratamento de manutenção em doentes adultos com doença pulmonar obstrutiva crónica (DPOC) moderada a grave, que não estejam adequadamente tratados com uma associação de um corticosteroide para inalação e um agonista beta-2 de longa duração de ação ou uma associação de um agonista beta-2 de longa duração de ação e um antagonista muscarínico de longa duração de ação (ver RCM para informação sobre efeitos sobre o controlo dos sintomas e prevenção das exacerbações). **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Adultos A dose máxima recomendada é uma inalação 1x/dia, à mesma hora em cada dia. Doentes idosos, Compromisso renal e Compromisso hepático Não é necessário ajustar a posologia. Utilizar com precaução em doentes com compromisso hepático moderado a grave. População pediátrica A utilização não é relevante na população pediátrica (<18 anos) para a indicação de DPOC. Modo de administração Via inalatória. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram nasofaringite, cefaleia e infeção das vias respiratórias superiores. **Infeções e infestações** Frequentes Pneumonia, infeção das vias respiratórias superiores, bronquite, faringite, rinite, sinusite, gripe, nasofaringite, candidíase da boca e da garganta e infeção do trato urinário Pouco frequentes Infeção viral das vias respiratórias superiores **Doenças do sistema imunitário** Raros Reações de hipersensibilidade, incluindo anafilaxia, angioedema, urticária e erupção cutânea **Doenças do sistema nervoso** Frequentes Cefaleia **Afeções oculares** Desconhecido Visão turva **Cardiopatas** Pouco frequentes Taquiarritmia supraventricular, taquicardia e fibrilhação auricular **Doenças respiratórias, torácicas e do mediastino** Frequentes Tosse e dor orofaríngea Pouco frequentes Disfonia **Doenças gastrointestinais** Frequentes Obstipação Pouco frequentes Boca seca **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia e dorsalgia Pouco frequentes Fraturas **TITULAR DA AIM** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** setembro 2020. Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Medicamento sujeito a receita médica. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial- Portela & Cº, S.A., À Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. **DMgMA_PT201019**

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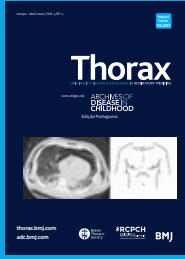
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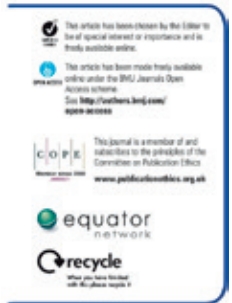
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Editorial

No último trimestre, numa fase muito complicada da pandemia, acendeu-se uma nova esperança com a chegada das primeiras vacinas contra a COVID-19. O resultado da ampla imunização da população deu uma nova esperança a toda a sociedade. Iniciado o processo de vacinação, cedo surgiram relatos da ocorrência de reações adversas, na sua maioria relacionadas com o processo fisiológico de aquisição de imunidade. Mas também foram descritas reações alérgicas e não alérgicas, por vezes graves, felizmente pouco frequentes.

Instalou-se a preocupação e a dúvida começou a circular em especial entre os alérgicos. Deviam ou não ser vacinados? Foram muitos os doentes que imediatamente contataram as equipas de saúde. Seria melhor esperar? A vacina estaria contraindicada?

Em geral a resposta foi garantir que quase todos os alérgicos podem ser vacinados com toda a segurança, não devendo ser esta uma barreira, sendo definidos critérios de avaliação e locais diferenciados de administração. E quando se continuou a aplicação maciça de vacinas, tal como também seria previsível, foram reportadas algumas outras reações adversas, nomeadamente da coagulação. E, apesar de terem ocorrido com uma frequência inferior à esperada para a população em geral, levou à decisão pelas autoridades de interromper durante algum tempo a administração de uma das vacinas.

Como profissionais de saúde devemos fornecer uma análise clara e baseada na evidência sobre os riscos e os benefícios de ser vacinado. É imperioso que a notificação sistemática das reações adversas às vacinas contra a COVID-19, permita identificar o reduzido grupo de doentes para os quais estas vacinas estarão contraindicadas, não excluindo assim os que podem adquirir proteção contra esta infeção de elevada morbidade e considerável letalidade.

Nas instalações em que as vacinas são administradas deve respeitar-se um intervalo mínimo de vigilância, que em Portugal se definiu corretamente em 30 minutos, permitindo identificar e tratar imediatamente, por exemplo, os casos de anafilaxia com adrenalina intramuscular. Um adequado sistema de farmacovigilância irá assegurar a segurança de um programa de vacinação que requer celeridade para alcançar um êxito significativo.

Relacionado com a pandemia, neste número da revista trazemos para Vossa apreciação um estudo transversal de Shields e colaboradores, “Seroprevalência e carga assintomática do vírus SARS-CoV-2 em profissionais de saúde”, no qual se identificaram diferenças no risco ocupacional de exposição ao SARS-CoV-2 entre diferentes departamentos hospitalares, confirmando a ocorrência de seroconversão assintomática nos profissionais de saúde, sugerindo mais investigação que possa influenciar as práticas futuras de controlo de infeção e de saúde ocupacional.

Também a adequada gestão das agudizações asmáticas, que estão associadas a elevada morbidade desta doença crónica prevalente em todos os grupos etários e uma associação direta entre a morbidade da asma e o insucesso escolar, que poderá ser prevenido através de medidas de apoio educacional, são discutidas nesta edição. Sinha e colaboradores, num artigo de revisão, discutem estratégias que permitam capacitar as crianças e os jovens asmáticos no sentido de uma tomada de decisão partilhada e da autogestão, ajudando a minimizar o impacto da asma na sua vida; os autores consideram que apesar das evidências de apoio a estas estratégias sejam escassas ou heterogéneas, novas abordagens tecnológicas poderão ajudar a capacitar quer os jovens asmáticos, quer os que sofram de outras condições de saúde crónicas.

Investigação sobre um modelo de estratificação do risco de cancro de pulmão do *Liverpool Lung Project*, visando contribuir para a sua deteção precoce e um estudo europeu de colaboração sobre a sobrevivência a longo prazo após início de ventilação não invasiva domiciliária, ocupam as páginas finais deste número, merecendo igualmente uma leitura atenta.

“Last but not least” gostaríamos de agradecer reconhecidamente às empresas que se associam a esta publicação, viabilizando mais uma iniciativa de educação médica que nos parece ser de reconhecida relevância.

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A Ressonância magnética na doença pulmonar intersticial (RM-DPI): um impulso para inovar o diagnóstico pulmonar

Pierluigi Ciet^{1,2}

A prevalência da doença pulmonar intersticial (DPI) é elevada e está a aumentar progressivamente.¹ A mortalidade e a morbilidade variam de acordo com o subtipo de DPI, mas a sobrevivência média global é fraca, variando entre 5 e 14 anos.² Independentemente da classificação e causa da fibrose pulmonar, vários doentes apresentam DPI de fibrose progressiva (DPI-FP), caracterizada por um rápido declínio da função pulmonar.³ Um estudo de referência recente demonstrou uma redução na progressão da doença DPI-FP utilizando medicamentos antifibróticos dispendiosos.⁴ Contudo, metade dos doentes com DPI não beneficiam destes medicamentos antifibróticos dispendiosos, mas poderiam receber um melhor tratamento com anti-inflamatórios ou tratamento combinado. Por conseguinte, existe uma necessidade não satisfeita de uma ferramenta de monitorização para os doentes com DPI, avaliando a quantidade de fibrose pulmonar e inflamação para orientar as escolhas de tratamento e monitorizar a resposta.³

A monitorização atual, nomeadamente a TAC de alta resolução (TAC-AR) e o teste de função pulmonar, não consegue diferenciar entre doença pulmonar fibrótica e inflamação ativa.^{3,5} A histologia pode fazer esta distinção, mas a biopsia é um procedimento de alto risco não realizado habitualmente em doentes com DPI. Em contrapartida, a RM do tórax pode oferecer uma solução completa para a DPI, fornecendo informação estrutural e funcional num único exame, tal como a RM de perfusão inflamação ventilação e estrutura (VIPS-MRI, do inglês *ventilation inflammation perfusion and structure magnetic resonance*).⁶ Utilizando a VIPS-MRI, tanto a fibrose pulmonar como a inflamação podem ser detetadas para selecionar o tratamento com a melhor relação custo-benefício e para monitorizar o seu efeito.⁷ Em linha com este conceito, no interessante artigo publicado na *Thorax* de Weatherley *et al* propuseram

uma avaliação de imagem semiquantitativa da perfusão pulmonar baseada na primeira passagem do agente de contraste à base de gadolínio utilizando a ressonância magnética dinâmica com contraste em coorte de doentes com DPI-FP.

O estudo compara a largura total a meio-máximo ($FWHM_{mean}$ *Full Width Half Maximum*) da curva de contraste dinâmica calculada sobre todo o pulmão como uma estimativa da resposta global da perfusão pulmonar à FPI e uma possível alteração da gravidade da doença entre o início do estudo e um estudo de seguimento de 6 meses. Uma segunda avaliação semiquantitativa do IQR da distribuição dos valores de FWHM sobre todo o pulmão (FWHM IQR) é utilizada como avaliação candidata da heterogeneidade da perfusão pulmonar. O estudo apresenta os primeiros resultados promissores e clinicamente relevantes da quantificação da perfusão pulmonar como avaliação da progressão da doença e da resposta ao tratamento na DPI-FP. São necessários novos biomarcadores para avaliar a progressão da DPI-FP nas fases iniciais da doença.³ Estudos anteriores sobre TC utilizando métodos quantitativos, como o CALIPER, demonstraram claramente a estreita relação entre a constrição vascular e a progressão da fibrose.⁸

A quantificação da vasculatura e perfusão pulmonar são, portanto, fortes preditores do resultado do doente na DPI-FP.⁹ Isto apoia fortemente um maior desenvolvimento da RM para avaliar a perfusão pulmonar como um possível biomarcador de progressão precoce na DPI-FP.⁷ Apesar da pequena coorte, a média FWHM demonstra uma repetibilidade razoável, que é determinante para a seleção de biomarcadores robustos, e que poderia ser ainda melhorada por um aperfeiçoamento do protocolo. Subsistem algumas incertezas. A utilização de um substituto semiquantitativo para perfusão pulmonar pode ser influenciada pelo débito cardíaco, que na população idosa com DPI-FP pode ser bastante variável, especialmente na presença de outra comorbilidade cardíaca.

O biomarcador proposto como indicador da heterogeneidade da perfusão demonstrou uma repetibilidade marginal, pelo que a $FWHM_{mean}$ parece ser um melhor candidato como biomarcador de imagem. Finalmente, não é claro se a diferença medida com a $FWHM_{mean}$ entre os dois pontos temporais está relacio-

nada com a progressão da fibrose e não com o reflexo de uma verdadeira lesão vascular subjacente. Portanto, o estudo de Weatherley *et al* pode gerar uma nova dinâmica para inovar o diagnóstico pulmonar da FWHM. Seria importante coordenar um esforço conjunto para um estudo multicêntrico num grupo devidamente selecionado de doentes com DPI-FP, incluindo avaliações da atividade da doença (por exemplo, Krebsvonden-Lungen 6, também conhecida como KL-6), resultados reportados pelos doentes (por exemplo, *King's Brief Interstitial Lung Disease*) e biomarcadores quantitativos de TAC-AR. Essa validação será crucial para introduzir a VIPS-MRI como uma ferramenta clínica para a DPI-FP.

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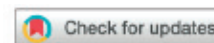
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REFERENCES

- Olson AL, Gifford AH, Inase N, et al. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. *Eur Respir Rev* 2018;27:180077.
- Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. *Respir Res* 2019;20:57.
- Cottin V, Wollin L, Fischer A, et al. Fibrosing interstitial lung diseases: knowns and unknowns. *Eur Respir Rev* 2019;28:180100.
- Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381:1718–27.
- Elicker BM, Kallianos KG, Henry TS. The role of high-resolution computed tomography in the follow-up of diffuse lung disease. *Eur Respir Rev* 2017;26:170008.
- Tiddens HAWM, Stick SM, Wild JM, et al. Respiratory tract exacerbations revisited: ventilation, inflammation, perfusion, and structure (VIPS) monitoring to redefine treatment. *Pediatr Pulmonol* 2015;50:S57–65.
- Romei C, Turturici L, Tavanti L, et al. The use of chest magnetic resonance imaging in interstitial lung disease: a systematic review. *Eur Respir Rev* 2018;27:180062.
- Jacob J, Bartholmai BJ, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. *Eur Respir J* 2017;49:1601011.
- Jacob J, Bartholmai BJ, Rajagopalan S, et al. Predicting outcomes in idiopathic pulmonary fibrosis using automated computed tomographic analysis. *Am J Respir Crit Care Med* 2018;198:767–76.

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Imagiologia funcional respiratória reestruturada para COVID-19

Josien van Es,¹ Lilian J Meijboom²

Thillai *et al*¹ descrevem um método de análise de imagens, a imagiologia respiratória funcional (FRI, do inglês *functional respiratory imaging*), que cria uma reconstrução tridimensional tanto das vias aéreas como da vasculatura pulmonar a partir de imagens de TAC, em 10 doentes com infeção grave por COVID-19. Calcularam a distribuição do fluxo sanguíneo pulmonar de acordo com o tamanho da área da secção transversal dos vasos e compararam os dados com a idade, sexo, altura e pré-morbilidade com doentes com Síndrome de Dificuldade Respiratória Aguda (SDRA) (n=7) e dados retrospectivos de voluntários saudáveis (n=107). Os resultados de imagem pós-processamento foram interessantes, uma vez que constataram que, em doentes com COVID-19, o fluxo sanguíneo diminuiu nos vasos periféricos de pequeno calibre e, ao invés, aumentou nas artérias mais centrais, quando comparado tanto com doentes com SDRA como com o grupo de controlo saudável, sem se observarem diferenças no tamanho do ventrículo direito.

Atualmente, estes dados constituem uma hipótese que origina mais do que uma base para interpretações clínicas ou mesmo alterações terapêuticas sobre o protocolo de tratamento atual. Os autores postularam que a troca gasosa deficitária observada na COVID-19 pode ser explicada pela redistribuição devido a microtrombos, vasoconstrição das artérias pulmonares distais ou a ambos. De facto, em doentes com COVID-19 admitidos em unidade de cuidados intensivos, a prevalência de (micro)trombos é inesperadamente elevada e a prevalência de

superinfecções bacterianas e fúngicas, nas quais se pode esperar uma vasoconstrição secundária, também é considerável, de 31% vs. 7,2%, respetivamente.^{2,3}

Para além de (micro)trombos ou vasoconstrição, outros mecanismos podem ser responsáveis pela redistribuição do fluxo sanguíneo, tais como o aumento da resistência capilar pulmonar, a disfunção endotelial capilar pulmonar e a apoptose associada (seja por infeção viral direta da célula endotelial ou por inflamação endotelial difusa mediada por imunidade), a infiltração perivascular de células T ou o angioedema pulmonar dependente de bradicinina.^{4,5}

Contudo, para interpretar corretamente a relevância desta perda de vasculatura, são necessárias informações clínicas e radiológicas suplementares, como o historial médico, incluindo anomalias radiológicas pré-existentes, e a presença atual de consolidações, opacidades de líquidos pleurais ou de “vidro fosco”, sendo que todas influenciam as trocas gasosas e, em particular, estas últimas, estando frequentemente presentes em doentes com COVID-19 grave.

Além das anomalias dos vasos que influenciam o fluxo sanguíneo, também os danos alveolares poderão ser causados por comorbilidade pulmonar (pré-existente) ou pela própria infeção COVID-19 com necrose das células de revestimento alveolar, hiperplasia pneumocitária tipo 2 e deposição de fibrina intra-alveolar linear.⁴ Com base nestes resultados, as opções terapêuticas como pressão positiva expiratória final, anticoagulação e vasodilatadores não podem ser recomendadas. De facto, estas últimas podem mesmo ser perigosas em caso de hipoxemia devido a problemas não vasculares, devido ao risco de *shunting*. Adicionalmente, o desenho do estudo merece alguma consideração. Em primeiro lugar, existiam apenas sete doentes não COVID com SDRA, pelo que a representatividade deste grupo pode ser questionável. Além disso, a causa subjacente à SDRA não era conhecida. Em

segundo lugar, desconhece-se ao certo se o protocolo e a qualidade dos exames de doentes com SDRA e COVID-19 e dos grupos de controlo foram semelhantes e como é que isso poderia influenciar as medições de SDRA.

Em conclusão, Thillai *et al* demonstraram de forma bem notória que os doentes com infeção por COVID-19 grave apresentam redistribuição do fluxo sanguíneo pulmonar. Estamos expectantes por saber mais desta técnica de FRI, de preferência acompanhada por mais informação radiológica e clínica e devidamente enquadrada em ensaio bem concebido.

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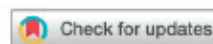
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REFERENCES

1. Thillai M, Patvardhan C, Swietlik EM. Functional respiratory imaging identifies redistribution of pulmonary blood flow in patients with COVID-19. *Thorax* 2021;76:182–4.
2. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–7.
3. Garcia-Vidal C, Sanjuan G, Moreno-García E, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clin Microbiol Infect* 2020. doi:10.1016/j.cmi.2020.07.041. [Epub ahead of print: 31 Jul 2020].
4. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120–8.
5. van de Veerdonk FL, Netea MG, van Deuren M, et al. Kallikrein-Kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. *Elife* 2020;9:e57555.

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ARTIGO ORIGINAL INVESTIGAÇÃO

Seroprevalência e carga assintomática do vírus SARS-CoV-2 em profissionais de saúde: um estudo transversal

Adrian Shields,^{1,2} Sian E Faustini,¹ Marisol Perez-Toledo,³ Sian Jossi,³ Erin Aldera,⁴ Joel D Allen,⁵ Saly Al-Taei,¹ Claire Backhouse,¹ Andrew Bosworth,² Lyndsey A Dunbar,¹ Daniel Ebanks,¹ Beena Emmanuel,¹ Mark Garvey,^{2,4} Joanna Gray,² I Michael Kidd,⁶ Golaleh McGinnell,² Dee E McLoughlin,⁷ Gabriella Morley,⁷ Joanna O'Neill,² Danai Papakonstantinou,⁴ Oliver Pickles,⁸ Charlotte Poxon,⁸ Megan Richter,¹ Eloise M Walker,⁴ Kasun Wanigasooriya,⁸ Yasunori Watanabe,^{5,9} Celina Whalley,⁸ Agnieszka E Zielinska,⁴ Max Crispin,⁵ David C Wraith,^{3,10} Andrew D Beggs,⁸ Adam F Cunningham,³ Mark T Drayson,^{1,10} Alex G Richter^{1,2}

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RESUMO

Objetivo Determinar as taxas de carga viral assintomática e seroprevalência de anticorpos SARS-CoV-2 em profissionais de saúde.

Desenho Um estudo transversal de profissionais de saúde assintomáticos, realizado em 24/25 de abril de 2020.

Local do estudo Hospitais Universitários de Birmingham NHS Foundation Trust (UHBFT), Reino Unido.

Participantes Foram recrutados 545 profissionais de saúde assintomáticos em serviço. Os participantes foram convidados a participar através dos meios de redes sociais dos UHBFT. Os critérios de exclusão incluíam sintomas atuais consistentes com a COVID-19. Não foram excluídos potenciais participantes.

Intervenção Os participantes forneceram uma zaragatoa nasofaríngea e uma amostra de sangue venoso que foram testadas para anticorpos contra o ARN de SARS-CoV-2 e anticorpos (glicoproteínas) neutralizadores da proteína da espícula SARS-CoV-2. Os resultados foram interpretados no contexto de doenças anteriores e dos departamentos hospitalares em que os participantes trabalharam.

Principal medida dos resultados Proporção de participantes que demonstram infecção e serologia positiva de SARS-CoV-2.

Resultados A prevalência pontual da carga viral de SARS-CoV-2 foi de 2,4% (n=13/545). A seroprevalência global de anticorpos contra a SARS-CoV-2 foi de 24,4% (n=126/516). Os participantes que reportaram doenças sintomáticas anteriores tiveram uma seroprevalência mais elevada (37,5% vs 17,1%, 2=21,1034, p<0,0001) e respostas quantitativamente superiores de anticorpos do que aqueles que permaneceram assintomáticos. A seroprevalência foi superior entre aqueles que trabalhavam nos serviços de limpeza e manutenção (34,5%), medicina aguda (33,3%) e medicina interna geral (30,3%), com taxas mais baixas observadas nos participantes que trabalhavam em cuidados intensivos (14,8%). A etnicidade BAME (do inglês *Black, Asian and minority ethnic* [negra, asiática e minorias étnicas]) foi associada a um risco significativamente superior de seropositividade (OR: 1,92, 95% IC 1,14 a 3,23, p=0,01). O trabalho na unidade de cuidados intensivos foi associado a um risco significativamente menor de seropositividade em comparação com o trabalho noutras áreas do hospital (OR: 0,28, 95% IC 0,09 a 0,78, p=0,02).

Conclusões e relevância Identificámos diferenças no risco ocupacional de exposição ao SARS-CoV-2 entre departamentos hospitalares e confirmamos a ocorrência de seroconversão assintomática nos profissionais de saúde. É necessária uma investigação mais aprofundada

Key messages

What is the key question?

► What are the rates of asymptomatic viral carriage and the seroprevalence of SARS-CoV-2 antibodies in UK healthcare workers?

What is the bottom line?

► In this study, the point prevalence of SARSCoV-2 viral carriage was 2.4% and the overall seroprevalence of SARS-CoV-2 antibodies was 24.4%.

Why read on?

► This study identifies differences in the risk of exposure of healthcare workers to SARS-CoV-2 between ethnic groups and between hospital departments; these findings may inform future infection control and occupational health policy.

destas observações para informar as práticas futuras de controlo de infeções e de saúde ocupacional.

INTRODUCTION

Healthcare workers are critical to the ongoing response to the SARS-CoV-2 pandemic. During the course of their work, they are exposed to hazards that place them at risk of infection.¹ Previous studies have shown infection rates of up to 14% in symptomatic and 7.1% in asymptomatic healthcare workers,^{2,3} which are higher than general population studies reported to date and suggest an occupational risk. Antibody responses have been demonstrated post infection with SARS-CoV-2, but it is not yet known whether these correlate with immunity, or how long antibody titres will be maintained. The magnitude of antibody responses appears proportional to age and severity of infection suffered.⁴ Asymptomatic seroconversion following exposure to SARS-CoV and SARS-CoV-2 have been documented in small cohorts; again the quality and longevity of these immunological responses are unknown.^{1,5}

Understanding the relationship between infection, symptomatology and the subsequent serological responses is critical to understanding herd immunity, vaccine deployment and safeguarding the workforce. Seroprevalence studies provide the foundation to inform this understanding.

University Hospitals Birmingham NHS Foundation Trust (UHBFT) is one of the largest hospital trusts in the UK with over 20000 employees delivering care to 2.2 million people per annum. We conducted a cross-sectional study of 554 staff at UHBFT to determine the point prevalence of infection and seroprevalence of SARS-CoV-2 antibodies in healthcare workers and their relationship to prior symptoms of COVID-19 and the hospital departments in which participants worked.

METHODS

A cross-sectional study of asymptomatic healthcare workers at UHBFT was undertaken, recruiting 545 individuals who were at work over the course of 24 hours between 24 and 25 April 2020. Initial invitation to participate in the study was made via social media. There was no predefined sample size; participants self-reported for enrolment. Individuals were excluded if they reported symptoms of COVID-19 on the day. Individuals self-isolating at home due to personal symptomatic illnesses or illnesses in household contacts in the previous 2 weeks were indirectly excluded from the study.

All individuals volunteered a nasopharyngeal swab for SARS-CoV-2 RNA detection and a venous blood sample for anti-SARS-CoV-2 spike glycoprotein serology, tested using an ELISA developed inhouse by the University of Birmingham Clinical Immunology Service. Detection of SARS-CoV-2 RNA was performed using real-time PCR (Viasure, CerTest Biotec) directed against the ORF1ab and N genes following guanidine isothiocyanate inactivation of nasopharyngeal swabs.⁶ Serological analysis was performed using a high-sensitivity ELISA developed inhouse by the University of Birmingham Clinical Immunology Service. Serological analysis was performed at biological containment level 2. High-binding plates (Greiner Bio-One) were coated with trimeric SARS-CoV-2 spike glycoprotein^{7,8} and blocked with StabilCoat solution (Sigma-Aldrich). Serum was prediluted 1:40 prior to analysis. A combined secondary layer containing horseradish peroxidase conjugated ovine polyclonal antibodies against IgG, IgA and IgM followed by 3,3',5,5'-tetramethylbenzidine development was used to detect the presence of antibodies. The cut-off for positivity on the ELISA was set at 2 SD above the mean OD450 of eight pre-2019 negative sera run independently across seven separate plates.

Prior validation of this assay has shown it demonstrates 100% sensitivity in individuals with PCR-proven disease 7 days post symptom onset (n=59 hospitalised, n=31 community) and 97.8% specificity based on 270 individual negative pre-2019 samples. Intra-assay coefficient of variation (CV%) is 1.58% and interassay CV% is 7.5% for negative controls and 17.3% for positive controls and 7.2% for controls running at the cut-off of positivity on the assay.

Participants were asked to retrospectively report any illnesses consistent with COVID-19 that they had suffered in the previous 4 months. Ethnodemographic data and their department of work were also recorded. UHBFT patient mortality data were sourced from NHS England and information on the total number of PCR-positive inpatients from the UHBFT infection control team. Indices of deprivation in participants' postcodes were sourced from 2019 UK Ministry of Housing, Communities and Local Government statistics.⁹

Data were analysed using Graph Pad Prism V.8.4.2. Categorical data were compared using the χ^2 test and optical density distributions using the Kruskal-Wallis test with Dunn's post-test comparison for symptomatic and asymptomatic groups. Seroprevalence data are expressed as a percentage, with binomial CI calculated using Wilson's method. Indices of deprivation were transformed using the function $[\log(R)/(32844-R)]$, where R represented the individual rank of a participant's postcode within the national data; these parameters were specified as deprivation scores; numerically lower values represent more

deprived postcodes. Unpaired, two-tailed t-tests were used to compare the means of the seropositive and seronegative populations of these data. Using intensive care as a reference population, the relative risk (RR) of seropositivity for individuals working in other specific departments was determined, and the 95% CI for this RR was determined using Koopman's asymptotic score method.

Univariate analysis and multiple logistic regression were performed using seropositivity as the outcome variable. Age, sex, ethnicity, Index of Multiple Deprivation score and the departments in which individuals worked were included as independent variables. In univariate analysis, categorical variables were compared using two-sided χ^2 tests, and OR was calculated using the Baptista-Pike method. In this analysis, the OR represents the odds of seropositivity for an individual working in that department compared with not working in that department. In multiple logistic regression involving continuous variables, the OR represents change in odds of seropositivity changes per each increasing year of age or increasing unit of deprivation score.

All participants provided written, informed consent prior to enrolment in the study

RESULTS

The point prevalence of PCR positivity in asymptomatic healthcare workers was 2.4% (n=13/545). Of these individuals, 15.4% (n=2/13) had detectable anti-SARS-CoV-2 antibodies in their serum and 38.4% (n=5/13) subsequently became unwell with symptoms consistent with COVID-19. Serum was available for analysis on 516 individuals, and 26.3% (n=136/516) of participants reported a prior illness consistent with COVID-19 (table 1). The overall seroprevalence across the cohort was 24.4% (n=126/516); individuals reporting a prior symptomatic illness had significantly greater seroprevalence than those who had remained asymptomatic throughout the time period assessed (36.8% vs 17.1%, $\chi^2=19.75$, $p<0.0001$) (figure 1A). Antibody responses in individuals who had experienced a prior symptomatic illness were quantitatively greater than those who remained asymptomatic (Kruskal-Wallis statistics 7.159, $p=0.02$, Dunn's post-test comparison of symptomatic vs asymptomatic individuals: mean rank difference 17.02, adjusted $p=0.02$) (figure 1B).

We explored the relationship between the timing of healthcare worker illness associated with seropositivity and weekly trust-wide COVID-19 mortality, as a surrogate of overall patient burden (figure 1C). Illnesses associated with positive serology were occurring for over 3 weeks prior to UK lockdown. The temporal pattern of reported symptomatic illnesses associated with seropositivity in healthcare workers preceded that of trustwide deaths by approximately 1 week. The highest incidence of symptomatic illness associated with seropositivity (77.8%, n=14/18) was observed in the week beginning 28 March 2020, 1 week before peak weekly mortality was reached within UHBFT.

Seroprevalence was mapped to the departments where individuals work within UHBFT (figure 1D). Seroprevalence was highest in those working in housekeeping (34.5%, n=10/29), acute medicine (33.3%, n=10/30) and general internal medicine (30.3%, n=30/99) and lowest in participants working in intensive care (14.8%, n=9/61), emergency medicine (13.3%, n=2/15) and general surgery (13.0%, n=3/23). Using intensive care as a reference population, an increased RR of seropositivity was observed for those working in housekeeping (RR 2.34, CI 1.07 to 5.01, $p=0.03$), acute medicine (RR 2.25, CI 1.04 to 4.86, $p=0.04$) and general internal medicine (RR 2.05, CI 1.08 to 4.05, $p=0.03$).

Univariate and multivariate analyses were undertaken using serostatus as the dependent variable and incorporating participant age, sex, ethnicity, Index of Multiple Deprivation score of participants' postcodes and the hospital departments where participants worked as independent variables (table 2). Women

Table 1 Demographics of study participants

	All participants, n (%)	Seropositive, n (%)	Seronegative, n (%)	Seroprevalence (%)	P value
n	516	126	390	24.4	
Age (years)	42 (30–51)	41 (30–51)	42 (31–51)		0.48
Sex					
Male	128 (24.8)	24 (19.0)	104 (26.7)	18.8	0.09*
Female	388 (75.2)	102 (81.0)	286 (73.3)	26.3	
Ethnicity					
Asian British Bangladeshi	2 (0.4)	2 (1.6)	0 (0.0)	100.0	0.18†
Asian British Indian	25 (4.8)	6 (4.8)	19 (4.9)	24.0	
Asian British other/not stated	18 (3.5)	3 (2.4)	15 (3.8)	16.7	
Asian British Pakistani	11 (2.1)	4 (3.2)	7 (1.8)	36.4	
Black African	10 (1.9)	5 (4.0)	5 (1.3)	50.0	
Black British	17 (3.3)	5 (4.0)	12 (3.1)	29.4	
Filipino	21 (4.1)	6 (4.8)	15 (3.8)	28.6	
Mixed heritage	10 (1.9)	4 (3.2)	6 (1.5)	40.0	
Not disclosed	74 (14.3)	15 (11.9)	59 (15.1)	20.3	
Other	13 (2.5)	5 (4.0)	8 (2.1)	38.5	
White Irish	5 (1.0)	1 (0.8)	4 (1.0)	20.0	
White other	25 (4.8)	4 (3.2)	21 (5.4)	16.0	
White British	285 (55.2)	66 (52.3)	219 (56.2)	23.2	

P values pertain to analysis of differences between seropositive and seronegative groups.

Median and IQR are provided.

* $\chi^2=16.25$, df=12.

† $\chi^2=2.964$, df=1, Z=1.722.

had a higher seroprevalence than men (26.3% vs 18.8%), but this difference was not statistically significant in univariate or multivariate analysis (adjusted OR: 1.49, 95%CI 0.81 to 2.83, $p=0.07$). Univariate and multivariate analyses both demonstrated individuals of BAME (Black, Asian and minority ethnic) ethnicity were at significantly greater risk of seropositivity than individuals of white ethnicity (adjusted OR: 1.92, 95%CI 1.14 to 3.23, $p=0.01$). Working in intensive care medicine was associated with significantly reduced risk of seropositivity in multivariate analysis (adjusted OR: 0.28, 95%CI 0.09 to 0.78, $p=0.02$).

On average, the Index of Multiple Deprivation score was significantly lower in the home postcodes of BAME participants compared with white participants (−0.570 vs −0.232, $t=3.747$, $p=0.0002$). However, no significant differences between any individual government indices of deprivation were observed between individuals who were seropositive and seronegative in this study (table 3). Furthermore, in multiple logistic regression analysis, the Index of Multiple Deprivation did not influence serostatus in this study (OR 0.99, 95%CI 0.7387 to 1.323, $p=0.9503$). This supports an interpretation that the observed difference in seroprevalence rates in this cohort is more likely due to occupational risk, rather than external factors.

DISCUSSION

In this cross-sectional study of asymptomatic healthcare workers, the point prevalence of SARS-CoV-2 nasopharyngeal carriage (2.4%) was concordant with a contemporaneous UK study² but less than an earlier study performed during the peak of the pandemic (cumulative total 14.0%).³ The relatively low prevalence of viral RNA carriage in our cohort appears to be in keeping with the national epidemiology of the first wave of the UK SARS-CoV-2 epidemic. In contrast, we report a higher overall SARS-CoV-2 seroprevalence of 24.4%. This suggests the cumulative infection rate determined using molecular testing should have been far higher than was reported in previous studies.^{2,3} This is consistent with data demonstrating the relative insensitivity of nasopharyngeal swabs in determining viral carriage,^{5,10} but may also reflect access to testing. With respect to the assay used to determine seropositivity, the coefficient of variance of internal quality control material designed to run close to the clinical cut-off of the assay was 7.2%, suggesting that true seroprevalence lies between 23.8% and 26.0% based on the data from our cohort. Thus, the over-

all seroprevalence of SARS-CoV-2 antibodies in healthcare workers in this study is significantly greater than the 6% seroprevalence in the general population of the Midlands region determined by Public Health England.¹¹ Data from two other studies also found elevated infection or seroprevalence in healthcare workers compared with the general population.^{12,13} Collectively, these studies suggest a marked occupational risk of exposure to SARS-CoV-2 associated with healthcare work during the COVID-19 pandemic.

We identify variation in the seroprevalence of SARS-CoV-2 antibodies among different groups of healthcare workers. The highest seroprevalence was observed in housekeepers (34.5%) and those working in acute medicine (33%) or general internal medicine (30.3%), with lower seroprevalence among participants working in intensive care medicine (14.8%). Multiple logistic regression confirmed a significantly lower risk of seropositivity in individuals working in intensive care medicine. This strongly supports the conclusion that differential risk of SARS-CoV-2 exposure exists within the hospital environment. The reasons underlying this are likely to be multifactorial: in accordance with national guidelines, intensive care units were designated high-risk environments and the use of enhanced personal protective equipment (PPE) including filtered face piece (class 3) respirators mandated. In contrast, fluid-resistant surgical masks were recommended in other clinical areas. The contribution of enhanced PPE in protecting staff from infection with SARS-CoV-2 should be studied further, including the availability of training, space and supervision to use PPE effectively. Differential occupational exposure to severe respiratory viruses was previously observed during the 2003 SARS-CoV outbreak.¹⁴

We demonstrate that BAME ethnicity confers a significantly increased risk of seropositivity in this study. Although individuals of BAME ethnicity within this study, on average, lived in significantly more deprived areas, the Index of Multiple Deprivation score of participants' home postcode did not significantly influence serostatus within our multiple logistic regression model. It is not clear from our study whether this increased risk of seropositivity arises from a greater risk of exposure to the virus, or a greater risk of infection if exposed to the SARS-CoV-2 virus. Regardless of the cause, this finding demands urgent further investigation, particularly in view of the ethnic disparities in the outcome from COVID-19.¹⁵

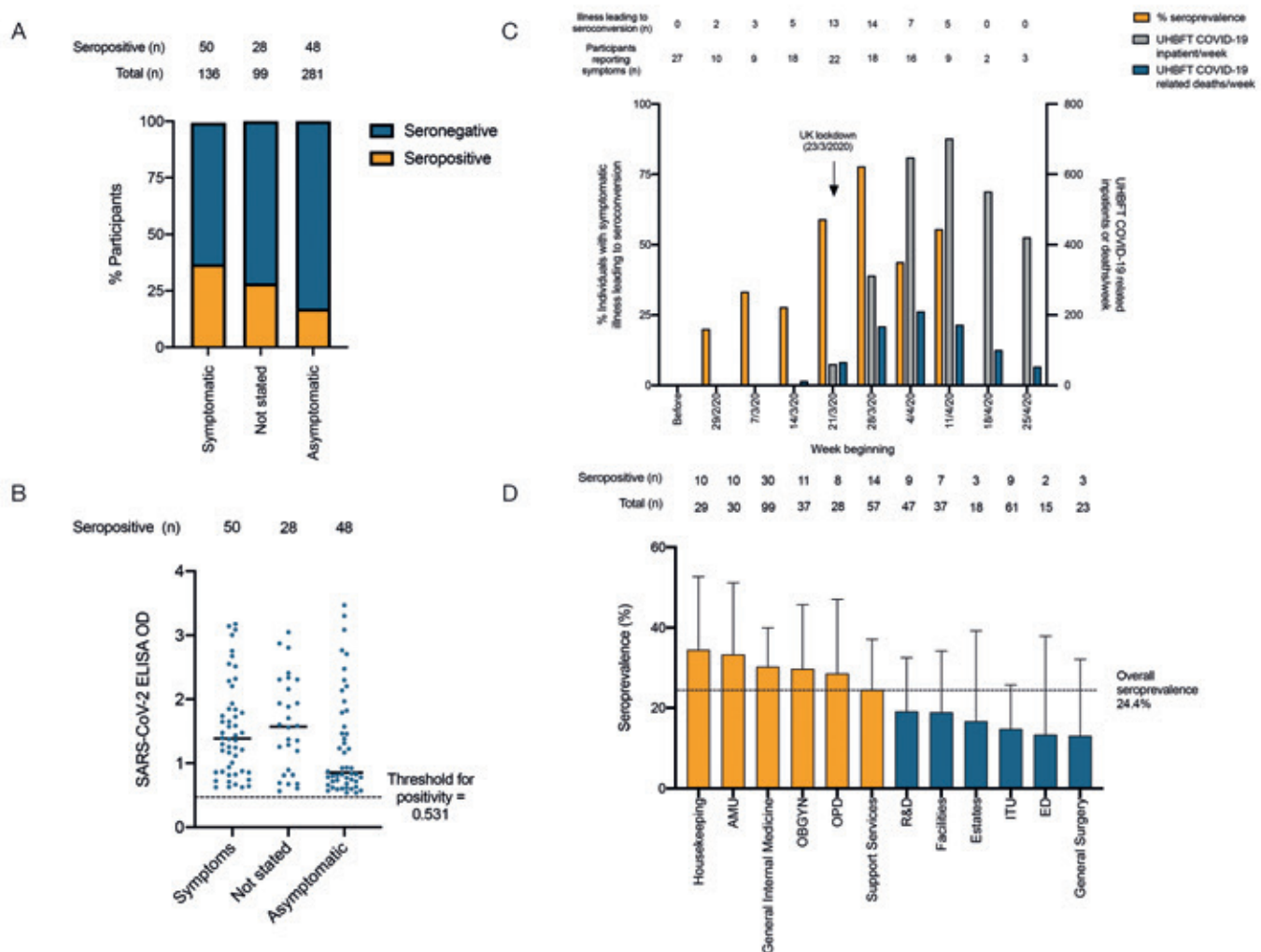


Figure 1 (A) Seroprevalence rates in study participants self-reporting prior symptomatic illnesses consistent with COVID-19 compared with asymptomatic individuals. (B) Optical density (OD) of anti-SARS-CoV-2 antibodies in individuals with positive serology classified by self-reported prior symptomatic illness ($n=126$). Line shows the median value of each group. (C) Timing of prior symptomatic illness in study participants and their relationship with seroprevalence of SARS-CoV-2 antibodies, total inpatients at UHBFT who had tested positive for SARS-CoV-2 by PCR and overall UHBFT-wide deaths in the weeks of March and April 2020. (D) Seroprevalence of SARS-CoV-2 antibody in study participants by department in which they work. AMU, acute medical unit; ED, emergency department; ITU, intensive care unit; OBGYN, obstetrics and gynaecology; OPD, outpatient department; R&D, research and development; UHBFT, University Hospitals Birmingham NHS Foundation Trust.

We demonstrate viral carriage in 2.4% of asymptomatic participants and positive SARS-CoV-2 serology in the absence of prior symptomatology in 17.1%. Using similar immunological methods, Hains *et al*⁵ reported seroconversion in 44.0% ($n=11/25$) of healthcare workers in a US

dialysis unit, including asymptomatic seroconversion. It is not known whether asymptomatic viral carriage leads to transmission in the hospital setting and it is not possible to interrogate this retrospectively. However, our data would support the assessment of widespread healthcare worker tes-

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.

Table 3 Indices of deprivation scores associated with home postcode of study participants

Index of deprivation	Seropositive	Seronegative	P value
Index of deprivation	-0.395 (0.89)	-0.345 (0.79)	0.58
Income	-0.352 (0.99)	-0.316 (0.80)	0.69
Employment	-0.267 (1.00)	-0.312 (0.78)	0.61
Education and skills	-0.149 (0.87)	-0.160 (0.76)	0.90
Health and disability	-0.361 (0.73)	-0.347 (0.60)	0.84
Barriers to housing and services	-0.446 (0.57)	-0.333 (0.60)	0.07
Living environment	-0.433 (0.78)	-0.444 (0.71)	0.88
Income deprivation affecting children	-0.381 (0.93)	-0.333 (0.80)	0.59
Income deprivation affecting older adults	-0.369 (0.88)	-0.274 (0.75)	0.25

Mean and SD (in parentheses) are provided. Numerically lower values represent more deprived postcodes.

Means of seropositive and seronegative groups were compared using the unpaired, twotailed Student's t-test.

ting, including track and trace, on viral transmission during future waves of a pandemic.¹⁶

Finally, in keeping with previous studies that have correlated the severity of COVID-19 with the magnitude of the consequent antibody response,⁴ we demonstrate that antibody responses were, on average, significantly greater in individuals with prior symptomatic illness compared with those who remained asymptomatic. Further studies must determine the neutralising capacity of antibody responses associated with different severities of disease, the titres at which neutralising antibodies provide protection against infection and the duration of that protection.

There are a number of limitations to our cross-sectional study. Participants self-presented to enrol, which may introduce bias in the study cohort; however, the balance of participants working in intensive care, acute medicine and general internal medicine represents a fair reflection of front-line staff caring for patients with COVID-19. Both acute and non-acute, non-patient-facing occupational groups were recruited to enable comparison. Data were not available to determine how representative our sampling was through comparison of the numbers recruited to individual groups with the total number of staff at work on the day of the study. By failing to capture more recent infections leading to seroconversion, this may underestimate the true seroprevalence, although this study would have captured the peak of the pandemic. The relationship between symptomatic illness and antibody positivity requires confirmation in larger studies, particularly given that 19.2% (n=99/516) of participants did not provide information about whether they had suffered a prior symptomatic illness before serological analysis was undertaken. Further studies are necessary to consider whether the increased risk of seropositivity observed within individuals of BAME ethnicity is homogeneous throughout the individual ethnic populations that collectively constitute the BAME group.

Finally, longitudinal studies will be required to demonstrate the persistence of current seropositivity and to directly attribute seroconversion events to PCR-proven SARS-CoV-2 infection. In conclusion, we document the high seroprevalence of SARS-CoV-2 antibodies in healthcare workers with and without prior symptomatic illness and identify the groups of workers who have significantly different seroprevalence, suggesting differential occupational risk.

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Contributors AS helped conceive the study, collated and analysed the data, produced the figures, and wrote and revised the manuscript. SEF helped conceive the study, performed the experiments, and collated and analysed the data. MP-T and SJ performed the experiments, and collated and analysed the data. JDA, YW and MC produced the original trimeric spike-glycoprotein on which the serological assays are based and advised on methodology. JG, GoM and JON recruited participants to the study, facilitated the acquisition of clinical samples and collated the study results. MG collated and interpreted trust-level data on infections within UHBFT inpatients. IMK, AB and ADB supported the establishment and validation of the PCR workflow at the University of Birmingham. EA, DEM, GaM, DP, EMW and AEZ facilitated the establishment of RNA extraction and viral inactivation workflow within the category 3 biosafety laboratory at the University of Birmingham. KW, OP, CP and CW undertook PCR assays for the study. SA-T, CB, LAD, DE, BE and MR processed the samples, undertook the experiments and collated the results for serological studies. DCW, AFC and MTD helped conceive the study and supervised the analysis of data from the study. AGR is the senior and corresponding author for this manuscript and provided overall leadership for all aspects of the study. All authors helped revise the manuscript for publication.

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REFERENCES

- Chen W-Q, Lu C-Y, Wong T-W, et al. Anti-Sars-Cov immunoglobulin G in healthcare workers, Guangzhou, China. *Emerg Infect Dis* 2005;11:89-94.
- Treibel TA, Manisty C, Burton M, et al. COVID-19: PCR screening of asymptomatic health-care workers at London Hospital. *Lancet* 2020;395:1608-10.
- Hunter E, Price DA, Murphy E, et al. First experience of COVID-19 screening of healthcare workers in England. *Lancet* 2020;395:e77-8.
- Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa344. [Epub ahead of print: 28 Mar 2020].
- Hains DS, Schwaderer AL, Carroll AE, et al. Asymptomatic seroconversion of immunoglobulins to SARS-CoV-2 in a pediatric dialysis unit. *JAMA* 2020. doi:10.1001/jama.2020.8438. [Epub ahead of print: 14 May 2020].
- Bosworth A, Whalley C, Poxon C, et al. Rapid implementation and validation of a coldchain free SARS-CoV-2 diagnostic testing workflow to support surge capacity. *J Clin Virol* 2020;128:104469.
- Watanabe Y, Allen JD, Wrapp D, et al. Site-specific glycan analysis of the SARS-CoV-2 spike. *Science* 2020;369:eabb9983.
- Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020;367:1260-3.
- Ministry of housing, communities and local government, English indices of deprivation 2019.
- Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020;323:1843-4.
- Public Health England. Sero-surveillance of COVID-19, Weekly coronavirus disease 2019 (COVID-19) surveillance report, week 22, 2020.
- Houlihan C, Vora N, Byrne T, et al. SARS-CoV-2 virus and antibodies in front-line health care workers in an acute hospital in London: preliminary results from a longitudinal study. *medRxiv* 2020.
- Eyre DW, Lumley SF, O'Donnell D, et al. Differential occupational risks to healthcare workers from SARS-CoV-2: a prospective observational study. *medRxiv* 2020.
- Ip M, Chan PKS, Lee N, et al. Seroprevalence of antibody to severe acute respiratory syndrome (SARS)-associated coronavirus among health care workers in SARS and non-SARS medical wards. *Clin Infect Dis* 2004;38:e116-8.
- Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature* 2020.
- Black JRM, Bailey C, Przewrocka J, et al. COVID-19: the case for health-care worker screening to prevent Hospital transmission. *Lancet* 2020;395:1418-20.



A caminho de uma abordagem de tratamento personalizado para ataques de asma

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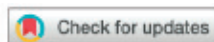
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RESUMO

Os ataques de asma (exacerbações) são comuns, sendo responsáveis por mais de 90000 internamentos hospitalares no Reino Unido anualmente. Causam a morte de quase 1500 pessoas por ano no Reino Unido, têm custos diretos e indiretos significativos e conduzem a uma perda acelerada e permanente da função pulmonar. O reconhecimento da asma como uma condição heterogênea com múltiplos fenótipos revolucionou a abordagem do tratamento a longo prazo da condição, com maior ênfase no tratamento personalizado e na introdução do conceito de características tratáveis. Em contrapartida, os ataques de asma estão mal definidos e mal compreendidos e a nossa abordagem de tratamento consiste em broncodilatadores e corticosteróides sistêmicos. Esta revisão pretende explorar as atuais limitações na descrição, avaliação e gestão das crises de asma. Iremos delinear os fatores de risco dos ataques e as estratégias para modificar esse risco e descrever as características reconhecidas dos ataques como um primeiro passo para o desenvolvimento de uma abordagem de fenotipagem e personalização do tratamento destes eventos de importância crítica. Assim, esperamos melhorar gradualmente o tratamento dos ataques de asma e reduzir os efeitos adversos associados a cursos recorrentes de corticosteróides.

INTRODUCTION

Asthma attacks (exacerbations) are common, accounting for over 90000 UK hospital admissions per annum.¹ They kill nearly 1500 people per year in the UK,² have significant associated direct and indirect costs³ and lead to accelerated and permanent loss of lung function.⁴

The recognition of asthma as a heterogeneous condition with multiple phenotypes has revolutionised the approach to the long-term management of the condition, with greater emphasis on personalised treatment and the introduction of the treatable traits concept.⁵ In contrast, asthma attacks are poorly defined and understood and our treatment approach consists of bronchodilators and systemic corticosteroids.

This review aims to explore the current limitations in the description, assessment and management of asthma attacks. We will outline the risk factors for attacks, strategies to modify this risk and describe the recognised characteristics of attacks as a first step towards the development of an approach for phenotyping and personalising the treatment of these critically important events. By doing this, we hope to gradually improve asthma attack treatment and reduce the adverse effects associated with recurrent courses of corticosteroids.

DEFINING ASTHMA ATTACKS

The Global Initiative for Asthma (GINA) 2019 definition states that asthma exacerbations are events that involve a progressive increase in symp-

Box 1 ATS/ERS statement definitions of severe and moderate asthma exacerbations⁷

► Severe asthma exacerbation: events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalisation or death from asthma. The definition should include at least one of the following:

a. Use of systemic corticosteroids (tablets, suspension or injection), or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.

b. A hospitalisation or emergency department visit because of asthma, requiring systemic corticosteroids.

► Moderate asthma exacerbation: events that should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe. Should include one or more of the following:

a. Deterioration in symptoms.

b. Deterioration in lung function.

c. Increased use of short-acting β -agonist bronchodilator.

These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalisation or emergency department visits for asthma.

toms (ie, dyspnoea, wheeze or chest tightness) and a progressive decrease in lung function that are 'sufficient to require a change in treatment'.⁶ This is based on the 2009 American Thoracic Society/European Respiratory Society (ATS/ERS) definitions of severe and moderate exacerbations (box 1) which are usually used when defining exacerbations as an outcome measure in clinical trials.⁷

This definition of a severe exacerbation is inadequate because the event is retrospectively defined by the treatment received, rather than by any intrinsic characteristics of the event itself. The requirement for systemic corticosteroids should not be the sole determinant of whether an event is a severe exacerbation as factors such as patients' and physicians' assessment of severity and the availability and affordability of medical help will also influence what treatment is received. A more objective definition of moderate exacerbations for use in clinical trials has been proposed but not validated⁸ and the ERS/ European Academy of Allergy and Clinical Immunology (EAACI) taskforce statement on severe exacerbations considered that the use of

Para citar: Martin MJ, Beasley R, Harrison TW, *et al.* Thorax 2020;75:1119–1129.

systemic corticosteroids for at least 5 days (rather than 3) may be more clinically relevant although this remains a largely subjective definition.⁹

An attempt to describe exacerbations in a more objective way has also been made in the development of a 'composite exacerbation endpoint' (CompEx) based on diary events recorded by asthma subjects during clinical trials.¹⁰ Peak expiratory flow rate (PEFR), reliever use, symptoms and awakenings are combined in an algorithm and added to severe exacerbations defined by corticosteroid use. This methodology detected almost three times as many events as corticosteroid use alone allowing a reduction in clinical study size due to greater power. Although the exact significance of the additional events captured and the criteria used to define them can be debated, seasonal variation in CompEx events was preserved, there was a reduction in geographical variation in event rates and treatment effect was preserved or increased suggesting the events are clinically important.¹¹

RISK OF ASTHMA ATTACKS

Attack rate

Recent epidemiological surveys of UK and US health records have reported asthma attack rates in unselected populations of asthma patients between 0.1 and 0.2 per patient per year.^{12–13} Attack rates increased with asthma severity to ~0.5/patient/year in severe asthma (GINA Step 5).¹² In a study of over 5000 patients, two-thirds of patients did not exacerbate over a 7-year period and half of those who exacerbated did so only once.¹³

Only 370 (0.7%) 'frequent exacerbators' (≥1 exacerbations per year) were identified most of whom (58%) had mild to moderate asthma. A study of ~2500 patients coded with asthma on highdose inhaled corticosteroid/long-acting β -agonist (ICS/LABA) therapy reported severe exacerbation rates around 0.67/patient/year.¹⁴

Risk factors for attacks

A number of risk factors for attacks have been recognised (table 1). The strongest of these is a previous attack, especially within the last 12 months.¹³ Though other factors are undoubtedly important in terms of future risk, these have not been consistently identified in all studies. Asthma severity based on GINA Step or degree of airway obstruction appears to be associated with attack risk, but taken alone it is not a strong predictor¹⁵ and frequently exacerbating patients and those admitted with severe life-threatening asthma attacks are more likely to have mild to moderate asthma.^{13,16} Similarly, there is an association between asthma control and attack risk but poor control does not have a high predictive value for future attack¹⁷; ICS/LABA maintenance and reliever therapy significantly reduces attack risk but may have less effect on daily symptoms compared with ICS/LABA and short-acting β -agonist (SABA) therapy.¹⁸ The strength of a previous attack as a risk factor for future attacks, in contrast to the inconsistencies of identified predictors for attack risk between different cohorts may imply a high degree of individual attack susceptibility determined by heterogeneous mechanisms. It has been suggested that serial measurements of airway obstruction, display 'self-similarity', that is, patterns of variability observed in previous measurements are a preserved characteristic of an individual's disease, which allow forecasting of future lung function and prediction of deteriorations.¹⁹ Techniques such as detrended fluctuation analysis of PEFR measurements have been used to calculate measures of temporal self-similarity which have demonstrated efficacy in predicting future attacks.²⁰

Risk stratification

Attack prevention has been recognised as a key priority by the latest GINA strategy.⁶ It has been suggested that an individual's risk of asthma attack should be profiled and quantified in a similar fashion to the profiling and modification of cardiovascular risk factors for myocardial infarction (MI).²¹ Using previously

Table 1 Previously identified risk factors for asthma attacks in adults

	Factor	Studies
Previous attacks	↑ Number of previous attacks/ED admissions/hospitalisations	22 25 83 89–91
Disease severity	↓ FEV ₁ /↑ airway obstruction ↑ GINA Step	23 89 90 23
Disease control	High Asthma Control Questionnaire score Poor asthma control	14 23 91 92
Treatment	↑ Reliever/SABA use ↑ Previous courses of oral corticosteroids Fixed dose steroid versus steroid in maintenance and reliever therapy Poor treatment adherence Incorrect inhaler technique Inhaler device polypharmacy Co-prescription of non-steroidal antiinflammatory drugs	23 89 89 90 93 94 83 95
Demographic factors	Female gender Increased age Ethnicity: Black	25 89 90 95 25 89 95 91
Comorbidities	Smoking Gastro-oesophageal reflux disease Rhinitis, nasal polyps, eczema Rhinitis Chronic sinusitis Obesity Depression Vocal cord dysfunction Obstructive sleep apnoea Recurrent respiratory infections	22 89 95 25 89 95–97 89 95 25 14 96 97 23 89 96 98 83 95 97 83 83 97 97
Inflammation/phenotype	↑ Blood eosinophil count ↑ Bronchodilator responsiveness	89 95 96 96

Listed studies: Fuhlbrigge *et al.*,¹⁰ Bateman *et al.*,²³ Patel *et al.*,⁹⁰ Blakey *et al.*,⁸⁹ Loymans *et al.*,²² TENOR,⁹¹ Kang *et al.*,²⁵ McDonald *et al.*,⁸³ Bateman *et al.*,⁹² Engelkes *et al.*,⁹³ Melani *et al.*,⁹⁴ Price *et al.*,⁹⁵ Denlinger *et al.*,⁹⁶ ten Brinke *et al.*,⁹⁷ Fitzpatrick *et al.*⁹⁸.

GINA, Global Initiative for Asthma; SABA, short-acting β -agonist.

identified risk factors (table 1), several exacerbation risk-scoring systems have been developed.^{17 22 23} However, a systematic review and attempt to externally validate existing scoring systems using primary and secondary care cohort data concluded their performance was not of a sufficiently high standard to be useful in clinical practice.²⁴

Partly this may be due to the significant heterogeneity in asthma populations studied. Different risk factors for attack are likely to be important in different severities or phenotypes of asthma.²⁵ For example, type-2 (T2) biomarkers were associated with exacerbation risk in severe refractory asthma but not in mild to moderate asthma.²⁶ Other reasons for the difficulty in identifying consistent risk factors for future attack may include: (1) the challenge in distinguishing between a 'true' asthma attack and a worsening of commonly related comorbidities such as chronic obstructive pulmonary disease (COPD)/vocal cord dysfunction/dysfunctional breathing, (2) the broad non-objective definition of an 'asthma exacerbation' and likely heterogeneity in the causal pathophysiology in comparison to the more consistent pathology underlying events such as an MI, (3) the infrequent occurrence of asthma attacks in many patients and relative lack of longitudinal data assessing attack risk beyond the course of a 12-month study period and (4) the possible (and understandable) over-representation in the literature of an exacerbation-prone phenotype who may have distinct mechanisms of disease (traits) compared with the majority of the asthma population.²⁷

Risk modification

Modification of attack risk may be achieved at a population level through therapeutic interventions known to reduce the overall attack risk which are summarised in table 2. Though a number of treatments are effective in reducing attack risk, the mechanisms by which they do this are poorly described and there are few clinically useful biomarkers to target treatment (theranostic biomarkers). Therefore, selection of appropriate interventions to minimise an individual's risk of attack when attending clinic is less established.

Rather than considering and treating asthma attacks as uniform events, a greater degree of complexity in their profiling is required to determine whether these events have distinct phenotypes or traits and, if so, whether these are related to the stable disease phenotype. Personalised risk profiling based on the phenotypes, and ultimately endotypes, of asthma in periods of stability and during attacks has the potential to markedly improve forecasting of an individual's attack risk and direct targeted intervention to mitigate this risk. Novel strategies including biomarker-based methods of attack risk profiling need further assessment.^{28–29}

Targeted biological treatment of persistent T2-high airway inflammation leads to significant reductions in attack frequency, but further studies are required to determine more precise theranostic biomarkers and improve specificity of treatment selection. Profiling of remaining attacks in these patients will lead to novel insights into mechanisms of exacerbation and should inform further treatment targeting to reduce attack frequency further still. Patients prone to viral attacks may require a different targeted approach to therapy; for example, results from clinical and mechanistic studies suggest omalizumab can reduce the seasonal peak in attacks thought to be secondary to viral infection by reducing susceptibility to respiratory viruses (table 2).^{30–31} Appropriate preventative treatment for T2-low attacks and those triggered by bacteria, pollution or other recognised triggers is unclear and requires further study.

HETEROGENEITY OF ASTHMA ATTACKS

To better define attacks we need to understand more about how these events can be described and categorised. Some of the previously identified determinable characteristics of attacks and their relation to underlying aetiology are now considered and summarised in figure 1.

Recognised attack 'triggers'

Several triggers for asthma attacks have been identified and discussed in detail elsewhere.³² This section will provide a brief summary of the main recognised triggers to contextualise further discussion regarding attack phenotyping.

Viruses

The presence of viral DNA has been detected in ~80% of adult asthma attacks³³ making them the most commonly identified trigger of exacerbations. Rhinoviruses (RV), particularly subtypes A and C are the most commonly detected organisms in adults,³⁴ followed by influenza virus, respiratory syncytial virus and coronavirus.³³ Subjects with asthma may be more susceptible to viral infections owing to impaired expression of interferons (antiviral cytokines), and there is ample in vitro evidence to support this hypothesis³⁵ although not all studies are concordant.³⁶

Allergens

Inhalation of allergens is undoubtedly an important factor in the development of asthma attacks and sensitisation to various allergens including cats, dust mites, mould and cockroaches has been recognised as a risk factor for acute presentation requiring emergency treatment of asthma.³⁷ Whether aeroallergen exposure at normal environmental levels in a sensitised individual is a sufficient independent stimulus to trigger a severe attack is more difficult to establish due to the inherent difficulties in verifying and quantifying personal levels of exposure. Indirect evidence for such an effect is provided by observations of seasonal peaks in exacerbation rates correlating with high grass pollen counts.³⁸ However, excluding the effects of other potential 'co-triggers'³⁹ in such studies is difficult. Epidemics of asthma attacks secondary to exposure of high doses of airborne allergen have been described including 'thunderstorm' asthma which occurs due to exposure to high levels of grass pollen in sensitised individuals.⁴⁰

Accumulating evidence suggests a synergistic effect between allergic sensitisation and viral infection in provoking attacks.³⁵

Bacteria

The frequency of asthma attacks triggered by bacterial infection is unclear. The atypical organisms *Chlamydophila* and *Mycoplasma pneumoniae* have been detected in widely varying proportions of asthma patients with acute asthma symptoms⁴¹ with this variation likely secondary to the differing serological testing methods used in these studies. More recent studies have isolated bacteria alone from sputum and nasopharyngeal swab samples in patients with severe asthma exacerbations in up to 45% of cases using PCR-based techniques.⁴²

The role of bacteria in asthma attacks is unlikely to be fully elucidated until unbiased whole genome sequencing studies of the airway microbiota are performed before, during and after attacks. Interactions between viruses and bacteria may be important in the development of an attack⁴³ and significant rates of bacterial/viral coinfection have been noted⁴² with some in vitro evidence demonstrating viral impairment of the antibacterial function of human alveolar macrophages.⁴⁴

Other potential triggers

Less commonly described triggers for attacks include exposure to non-steroidal anti-inflammatory drugs (NSAIDs) or high doses of inhaled irritants, air pollution, perimenstrual asthma, stress and treatment non-adherence.⁴⁵

Onset phase

Clinical observations

Clinical studies have described 'sudden-onset' attacks (presentation within hours of symptom onset) in 6%–20% of cases.^{46–49} Both 'sudden' and 'slow' onset groups report upper respiratory tract infections (URTIs) as exacerbation triggers in >75% of cases although the sudden-onset group more commonly reported exacerbations triggered by allergens, exercise or stress.⁴⁶ Some patients with rapid-onset exacerbations reported obvious triggers such as NSAIDs or respiratory irritants⁴⁸ which may trigger acute bronchospasm. Despite similar initial PEFs, patients with 'sudden-onset' exacerbations demonstrated a significantly larger improvement in PEF following initial treatment.⁴⁶ Other features of slow-onset and rapid-onset attacks from clinical studies and histology studies reviewing cases of fatal asthma^{50–53} are summarised in figure 2.

There are several difficulties in interpreting these studies including: the varying cut-off times used to distinguish fast-onset and slow-onset attacks, the reliance on patient-reported triggers for attacks with a lack of objective testing (particularly viral PCR), the lack of contemporaneous measures of airway inflammation and the difficulty in distinguishing rapid-onset asthma attacks from differential causes of acute dyspnoea such as vocal cord dysfunction. However, these studies are useful in highlighting the variation in the reported/perceived onset phase of attacks and that broadly two clinical attack phenotypes of fast-onset, fast recovery ($\leq 10\%$) and slower-onset, slower recovery ($\geq 90\%$) have been observed.

Observational studies

Detailed data characterising the physiological changes associated with attacks come from the Formoterol and Corticosteroids Establishing Therapy (FACET) study.⁵⁴ Severe exacerbations were defined as events requiring an investigator-prescribed course of oral corticosteroid (OCS) or a deterioration of morning PEF >30% from mean baseline on 2 consecutive days. On retrospective review of PEF data, a gradual reduction in PEF was observed from ~7 days prior to the 'peak' of the exacerbation with a more rapid fall (as per the PEF exacerbation definition) in the 2–3 days preceding peak exacerbation (figure 3). The worsening of symptoms demonstrated a similar pattern to PEF with β -ago-

Table 2 Preventative treatments to reduce risk of asthma attacks

Agent	Patient group/phenotype	Efficacy for attack reduction	Mechanisms for attack reduction	Theranostic biomarker
T2-targeted treatment				
ICS	Asthma (not phenotyped)	Exacerbation rate ↓ 50% versus placebo ⁹⁹	Reduces 'eosinophilic' exacerbations ICS dose titration according to sputum eosinophil count significantly reduces eosinophilic exacerbation frequency but the rate of non-eosinophilic exacerbations was unchanged. ⁹⁹	Sputum eosinophil count ¹⁰⁰
Omalizumab	Adults and children with moderate to severe asthma on ICS	Exacerbation odds ↓ 45% (absolute risk reduction 10%) over 16–60 weeks Meta-analysis (10 studies, n=3261) ¹⁰¹	Reduces IgE-mediated allergic inflammation blocks IgE–receptor interaction on mast cells, basophils and antigen-presenting cells by selectively binding free IgE. ¹⁰² Reduces susceptibility to viral exacerbations ^{30 31} Enhances interferon (IFN)-α responses to rhinovirus (RV) via an unknown mechanism, limiting viral replication and ↓ detection of RV in nasal mucus, ↓ duration and severity of RV infection and ↓ rate of RV-associated illness.	Some evidence suggests that high levels of T2 biomarkers more likely to respond ¹⁰³ though not all studies are concordant ¹⁰⁴
Mepolizumab (anti-IL-5)	Severe asthma Evidence of eosinophilic airway inflammation	Exacerbation rate ↓ 50% ¹⁰⁵	Reduces 'eosinophilic' exacerbations Exacerbations in mepolizumab patients associated with a lower sputum eosinophil count, fewer symptoms and a reduced OCS treatment response than comparative events in placebo group ¹⁰⁶ suggesting residual events consistent with 'non-eosinophilic' exacerbations. No evidence for specific benefit on viral exacerbations Not assessed in initial phase III studies. No effect on postinfective fall in lung function or loss of asthma control ¹⁰⁷ in patients with mild asthma experimentally infected with RV. Mepolizumab-treated patients had a significantly enhanced viral load in comparison to placebo group.	Blood eosinophils ≥0.15 x 10 ⁹ /L ¹⁰⁸
Dupilumab (anti-IL-4/IL-13 receptor)	Moderate to severe asthma and high T2 biomarkers	Exacerbation rate ↓ 50% ¹⁰⁹	No evidence for specific benefit on inflammatory exacerbation subtype Possible effect on viral exacerbations Trend towards lower rates of viral URTI, bronchitis and influenza in treatment group compared with placebo group	FeNO ¹⁰⁹ Blood eosinophils ¹⁰⁹
Other treatment				
LAMA, eg, tiotropium	Asthma (not phenotyped) E	Exacerbation risk ↓ 33% in addition to ICS ¹¹⁰	Unclear ? due to effects on airway inflammation/mucus hypersecretion ¹¹¹	None
LABA, eg, formoterol	Asthma (not phenotyped) E	Exacerbation risk ↓ ~50% in addition to ICS ¹¹²	Unclear ?synergistic effect with ICS on allergen-induced airway inflammation. ¹¹³	None
Leukotriene antagonists (montelukast)	Adults with asthma (not phenotyped)	Exacerbation odds ↓ 40% (compared with placebo) ¹¹⁴	Viral exacerbations Possible selective treatment benefit for viral exacerbations. ¹¹⁵	None
Azithromycin	Severe asthma noneosinophilic subgroup ¹¹⁶ Uncontrolled asthma: eosinophilic and noneosinophilic ¹¹⁷	Exacerbation/ LRTI rate ↓ by 0.6/6 months exacerbation rate ↓ by ~0.8/patient year	Unclear Various mechanisms proposed ¹¹⁸ including: → Antiviral effects. → Reduction in airway load of Haemophilus influenzae. → Reduced levels of gastro-oesophageal reflux.	None
Self-management plan (monitoring PEF/ symptoms with written action plan)	Adults with asthma (not phenotyped)	Risk of hospitalisation ↓ 36% compared with usual care ¹¹⁹	Based on early recognition of increasing symptoms or reduction in peak flow (figure 3) as trigger to escalate asthma management and reduce clinical severity of 'peak' attack.	Not applicable
Potential future treatments				
Tezepelumab (anti-TSLP)	Uncontrolled asthma: T2 high and T2 low subgroups	Exacerbation rate ↓ 62% ¹²⁰	No evidence for specific benefit on inflammatory exacerbation subtype Viral exacerbations Effect on virally induced exacerbations not assessed in trial. In vitro: TSLP released by airway epithelial cells infected by RSV promoting a T2 inflammatory response ¹²¹ suggesting suppression of this pathway may prove effective.	Effect regardless of T2 biomarker levels
Fevipirant and timapirant (prostaglandin D2 receptor antagonists)		Unknown (phase III study of fevipirant in progress)	Fevipirant significantly ↓ eosinophilic airway inflammation in patients with moderate to severe persistent eosinophilic asthma. ¹²² Timapirant resulted in a significant ↓ in the rate of respiratory tract infections, ¹²³ hence may be effective in reducing viral exacerbations.	? Sputum eosinophils

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IFN-α, interferon α; IL, interleukin; LABA, long-acting β-agonist; LAMA, long acting muscarinic antagonist; LRTI, lower respiratory tract infection; OCS, oral corticosteroid; PEF, peak expiratory flow rate; RSV, respiratory syncytial virus; RSV, respiratory syncytial virus; RV, rhinovirus; T2, type 2; TSLP, thymic stromal lymphopoietin; URTI, upper respiratory tract infection.

nist use increasing in a similar fashion. The exacerbation events felt to require OCS (~70% of total) were associated with more symptoms and smaller PEF changes (on average about half the magnitude) than those defined by PEF criteria (30%) meaning decisions to treat with OCS (making these events severe exacerbations by default) were mostly made on the basis of symptoms rather than 'objective' PEF criteria. It is possible some patients had an increased perception of symptoms with a lower relative change in PEF or that these two different definitions of exacerbation actually represent different 'types' of exacerbation with potentially different underlying pathology. It is worth considering, however, that the mean PEF, symptom and β-agonist data presented in the FACET study figures (figure 3) disguise marked individual variability between patients. This individual variability

in rescue inhaler use prior to exacerbation has been demonstrated in studies using electronic monitoring of β-agonist use.^{55 56}

A smaller study (n=41)⁵⁷ also monitored symptoms and PEF prior to exacerbations, defined as hospitalisations for asthma treatment, decrease in personal best PEF >30% or increased symptoms for >48hours with lack of response to usual medications and starting or doubling of ICS/OCS. In contrast to the FACET results, worsening symptoms occurred prior to a reduction in PEF. Investigators noted the lack of significant diurnal variation in PEF preceding exacerbation.

Another key study detailing the pattern of pathophysiological airway changes during exacerbation by Reddel et al⁵⁸ described marked differences in peak flow patterns between exacerbation episodes and periods of poor control. Exacerbation

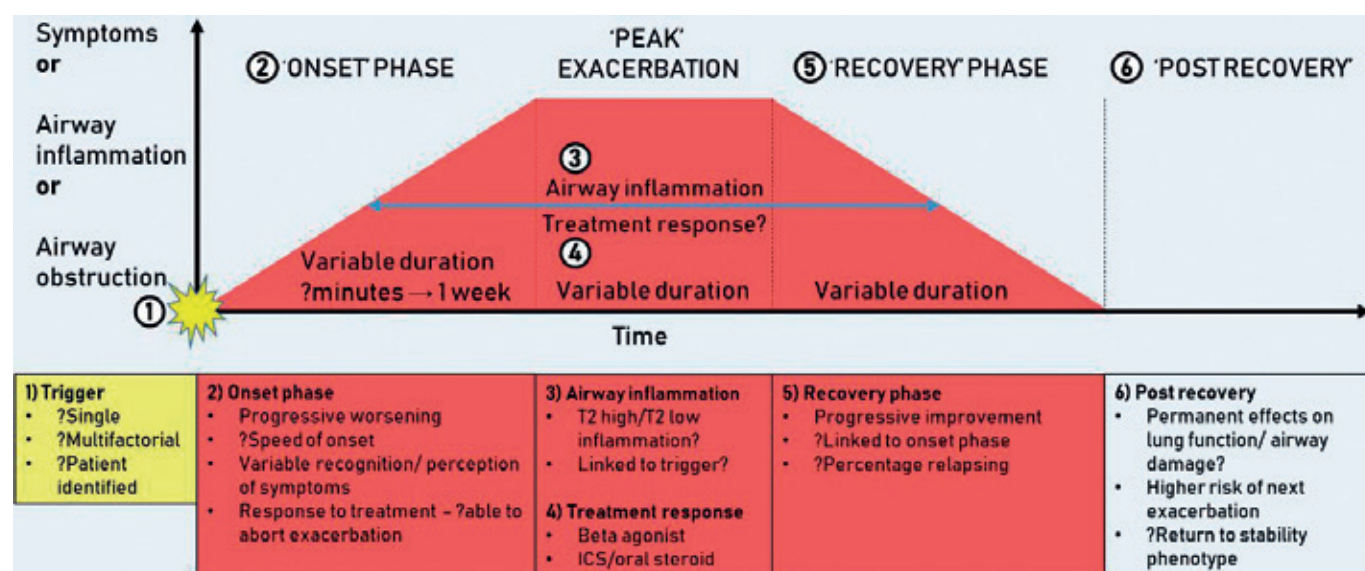


Figure 1 Summary figure illustrating determinable clinical, physiological and biochemical characteristics of asthma attacks. ICS, inhaled corticosteroid; T2, type 2.

was characterised by a linear fall in PEFR with little diurnal variability and an impaired β -agonist response compared with the high diurnal variability and bronchodilator reversibility seen during periods of poor control. Most of the exacerbations in this study were associated with symptoms of URTI although confirmatory viral PCR testing was not performed.

Viral attacks

Experimentally induced RV infections in patients with asthma resulted in significant reductions in PEFR and FEV₁, developing over a period of 6–7 days (figure 3)^{59,60} with worsening symptoms and an increase in airways hyper-reactivity⁵⁹ consistent with the study of Reddel *et al.*⁵⁸

Airway inflammation

Clinical observations

The inflammatory phenotypes of patients hospitalised with asthma attacks have been studied. Hasegawa *et al.*⁶¹ demonstrated 19/47 (40%) of such patients had a blood eosinophilia (blood eosinophil count $\geq 0.3 \times 10^9/L$) during their hospital admission although the clinical characteristics of this group and the 'non-eosinophilic' group were not significantly different. A cluster analysis of 218 Chinese patients hospitalised with exacerbations identified four distinct clusters.⁶² Two of

these demonstrated neutrophilic/mixed granulocytic airway inflammation in sputum cell counts in younger patients with early-onset asthma and mild airway obstruction (cluster 1; ~25%) and older lateonset patients with more severe airway obstruction (cluster 3; ~37%). The other two clusters had eosinophil predominant airway inflammation with cluster 2 (~22%) composed mostly of female patients with the most severe degree of airway obstruction post exacerbation and arterial hypoxia on admission and cluster 4 (~17%) composed exclusively of male smoking subjects. Unfortunately exacerbation triggers were not recorded and lung function and inflammometry measures were assessed at varying times (3–10 days) post exacerbation meaning at least 3 days of systemic steroid treatment had been administered prior to obtaining measurements/samples.

Bronchial biopsies from intubated patients admitted to ITU with sudden-onset severe exacerbations revealed markedly higher tissue densities of neutrophils and eosinophils in the epithelium and subepithelium than those seen in stable asthma and control groups.⁶³ A greater increase in neutrophils than eosinophils and greater expression of neutrophil chemoattractants (CXCL5&8) and their receptors (CXCR1&2) was observed. The disproportionate influx of neutrophils corresponds with the predominant neutrophilic inflammation noted in 'rapid-onset' cases of fatal asthma⁵²

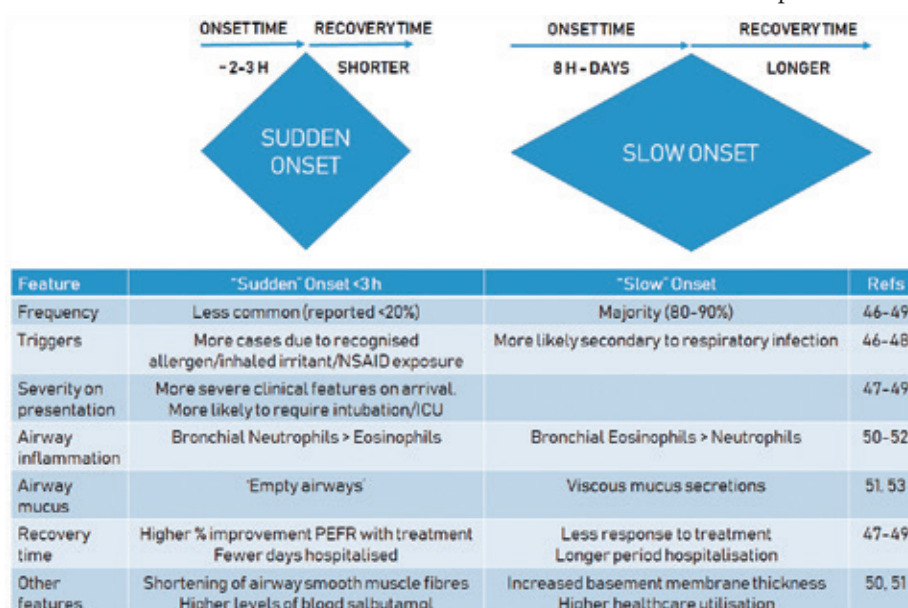


Figure 2 Asthma attack phenotypes noted from clinical observations/histological studies. 50–53 ICU, intensive care unit; NSAID, non-steroidal antiinflammatory drug; PEFR, peak expiratory flow rate.

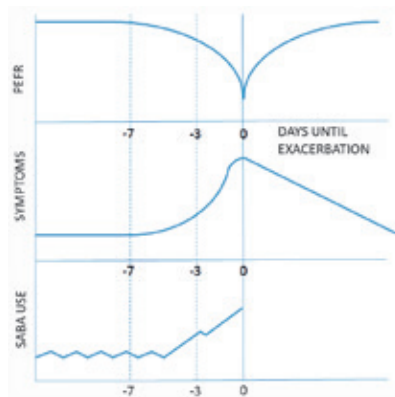


Figure 3 Composite diagram illustrating average observed changes in peak expiratory flow rate (PEFR), symptoms and short-acting β -agonist (SABA) use prior to attacks with peak of exacerbation occurring on day 0. Adapted from FACET (Formoterol and Corticosteroids Establishing Therapy),⁵⁴ Bardin *et al*,⁵⁹ Jackson *et al*⁶⁰ and Pilcher *et al*⁵⁵ studies.

and the inflammatory profile in bronchoalveolar lavage (BAL) from mechanically ventilated patients with severe asthma.⁶⁴ Again, the potential confounding effect on these results of high-dose steroid treatment causing a selective reduction in eosinophilic airway inflammation prior to sampling requires consideration.

Observational studies

Few data are available regarding the inflammatory nature of asthma attacks. In one study in adults assessing sputum differential counts, exacerbations were predominantly neutrophilic in nature (18/22, 82%).⁶⁵ The cause, however, was not clear as PCR for *Chlamydomydia pneumoniae* was negative in 99% of samples and no other pathogens were tested for. By contrast, a small study of adult patients hospitalised with exacerbations⁶⁶ reported 9/10 had sputum eosinophilia and demonstrated improvements with prednisolone treatment in FEV₁ and blood eosinophilia within 24 hours and sputum eosinophils within 48 hours. Another study of 18 patients with severe refractory asthma with exacerbations requiring OCS observed a significant overall increase in sputum eosinophils during exacerbation prior to OCS treatment with no change in sputum neutrophils. This was paralleled by mixed T helper (Th)1/Th2 activation during exacerbations (which was Th2-biased in the group at baseline) and further suppression of regulatory T cells (Tregs) compared with baseline.⁶⁷ Bjornsdottir *et al*⁶⁸ identified three distinct patterns of gene expression during exacerbation when compared with the stable state. One of these involved genes associated with innate immunity (despite no symptoms consistent with infection) with interleukin (IL) 15-mediated innate T-cell activation, the second was consistent with an allergen-driven immune response and the third expression profile differed least from the stable state and could not be attributed to a specific biological pathway. Jayaram *et al*⁶⁹ observed approximately equal numbers of eosinophilic (sputum differential $\geq 3\%$) and non-eosinophilic exacerbations in a group of 102 subjects with asthma while trying to minimise the ICS dose required to achieve good asthma control. The symptom burden associated with both exacerbation 'types' was the same, but non-eosinophilic exacerbations were associated with a less marked reduction in pre-bronchodilator FEV₁.

Experimentally induced exacerbations through withdrawal of steroid treatment have been studied using methods originally described by Gibson *et al*.⁷⁰ These studies, which included subjects on medium-dose to high-dose ICS70 and those with severe refractory asthma on high-dose ICS71 or oral steroids,⁷² generally demonstrated increases in sputum eosinophilia with steadily worsening symptoms. Increasing measures of airway obstruction (described as 'mild exacerbations') which peaked

between 2 and 6 weeks (variability that may have been related to differing rates of ICS/OCS withdrawal) were also observed.

These results suggest that uncontrolled eosinophilic inflammation eventually results in exacerbation-like events with a longer 'onset phase' than those provoked by viral infections. Results from these studies indicate that the inflammatory profiles of clinically observed asthma attacks are heterogeneous in nature. Further more detailed studies carefully assessing exposures/trigger factors are required and the resultant endotypic mechanisms underlying these heterogeneous phenotypes require further elucidation.

Viral attacks

Experimental RV infection has been demonstrated to induce neutrophilic airway inflammation in the asthmatic airways in the bronchial mucosa,⁷³ BAL⁷⁴ and sputum.⁷⁵ The degree of neutrophilic inflammation appears to be associated with levels of the neutrophil chemoattractant IL-8.⁷⁴ However, significant increases in eosinophil numbers in BAL⁷⁵ and bronchial mucosa⁷⁶ have also been observed during RV infection. More recent evidence suggests RV infection of bronchial epithelial cells may activate T2 inflammatory pathways through cytokines such as IL-25 and IL-33⁷⁷ causing release of mediators including IL-5 and IL-13 from T2 innate lymphoid cells and leading to augmentation of allergic inflammation and airway eosinophilia.⁷⁸

The results of these experimental studies, though important, may not reflect the complexity of the pathology underlying 'real-life' viral attacks. These can be caused by a number of different viruses in patients with more severe, uncontrolled asthma who may develop severe exacerbations rather than the mild to moderate exacerbation events (not requiring OCS treatment) usually observed in controlled conditions. Some studies of patients with asthma with confirmed 'wild-type' viral infections have reported these are associated with increased sputum neutrophil counts.^{79–80} Wark *et al*⁸⁰ reported patients with viral exacerbations had a greater degree of airway obstruction and risk of hospitalisation than those with non-infective exacerbations who were noted to have significantly increased sputum eosinophil counts. However, two studies by Bjerregard *et al*^{81–82} found no difference in the proportions of inflammatory phenotypes (eosinophilic vs non-eosinophilic) of patients with viral (PCR-positive) or non-viral (PCR-negative) exacerbations. In contrast to the findings above, patients with eosinophilic exacerbations had a significantly lower % predicted FEV₁ at baseline and were more likely to require supplemental oxygen.

Summary

Though data in this area are limited, these studies clearly demonstrate the variability in the phenotypes of attacks. Clinical observations suggest the rate of attack onset may vary and may depend on the initial trigger. Attacks secondary to known triggers such as viral infection vary in their inflammatory profile and this may be due to the interaction of the 'stable-state' inflammatory phenotype with the additional inflammatory burden induced during an attack. Larger scale studies attempting to objectively detail relevant trigger exposure, symptom perception, speed of onset and relevant biomarkers are required to allow more detailed phenotyping/endotyping of attacks.

Treatment response

The acute treatment of attacks corresponding to their identified phenotypic characteristics is summarised in table 3. Though extrapulmonary features may also be important in exacerbation,⁸³ they are not considered within the scope of this review.

Acute treatment: future directions

Currently, limited information is available to allow phenotypic specific treatment of acute asthma attacks and so systemic steroids and

Table 3 Acute treatment of asthma attacks

Attack phenotypic characteristic	Agent	Strategy	Patient group/phenotype (all with asthma ▲)	Efficacy for treatment of attacks	Mechanism for treatment effect
Airway obstruction	β_2 -agonists	Increasing dose	Adults	Recommended as part of acute treatment Increasing β_2 -agonist use described prior to hospital attendance with severe exacerbation ⁵⁶ Effectiveness of SABA ↓ during exacerbation	β -adrenergic receptor stimulation → smooth muscle relaxation → bronchodilation Loss of effectiveness of SABA during attack: → Subgroup of patients (<33%) with poor PEFR response to salbutamol described with ↑ airway obstruction, ↓ symptom duration and ↓ healthcare utilisation ¹²⁴ → ↓ β_2 -agonist FEV ₁ response during exacerbations—during viral exacerbations β_2 -adrenoceptor function is impaired ⁵⁸
	Short-acting anticholinergics	Systematic review: inhaled anticholinergics + β_2 -agonists in emergency management of asthma ¹²⁵	Adults	Recommended in acute severe asthma Risk of admission ↓ 28%	Decreased cholinergic tone → smooth muscle relaxation → bronchodilation
	Magnesium	Systematic review: intravenous magnesium sulfate in acute asthma ¹²⁶	Adults	Recommended in acute severe asthma with poor initial response to inhaled bronchodilators odds of admission ↓ 27% (significant study heterogeneity/threshold for magnesium unclear)	Smooth muscle relaxation → bronchodilation
Airway inflammation	Inhaled steroids	Doubling dose: ↓ Based on symptom score, PEFR <80% ¹²⁷ ↓ Based on symptom score, morning PEFR ↓ ≥15% ¹²⁸ Quadrupling dose during deteriorations in asthma control ⁸⁴ Quintupling ICS dose for 7 days at the early signs of loss of asthma control ¹²⁹ Systematic review ¹³⁰ : pre-emptive high-dose ICS in viral wheeze/asthma episodes (vs placebo) Pooled RCT data ¹³¹ : inhaled budesonide/formoterol (SMART) versus fixed ICS strategy (assumption SMART group ↑ ICS dose during attack via ↓ reliever use)	Age ≥13 years Attack within ≤12/12 Age ≥16 years Attack within ≤12/12	No effect on requirement for OCS No effect on requirement for OCS	No treatment effect observed
		Meta-analysis ¹³² : systemic corticosteroids versus systemic corticosteroids + ICS for acute asthma treatment in ED	Adults Attack within ≤12/12 5–11 year old children	Chance of exacerbation over 12-month period (hazard rate) ↓ 20% No effect	Unknown No treatment effect observed
		Cochrane review ¹³³ : early ED treatment of acute asthma with systemic corticosteroids	Children ≤6 years with intermittent asthma/viral triggered wheeze n=422 Child and adult patients step 2–4 treatment ≥1 attack in last 12/12 Suboptimal control during run-in. n=12 507	Exacerbation rate ↓ 35% ↓ 36% in 'cold-related' exacerbations with SMART versus other strategies	Reduction in (likely) virally triggered exacerbations Mechanism unclear Reduction in (likely) virally triggered exacerbations Mechanism unclear
	Oral steroids	Cochrane review: steroids to prevent relapse post-attack ¹³⁴	Child and adult patients admitted to ED with acute asthma 25 studies, n=2733	Odds of admission ↓ 27%	Unknown
			Child and adult patients, n=863 6 trials, n=374	Odds of admission ↓ 60% Odds of relapse in week postexacerbation ↓ 62%	Unknown
Airway infection	Antibiotics	Cochrane review ¹³⁵ : antibiotics for exacerbations of asthma	6 studies (3 adult and 3 children aged 1–18 years), n=681	No effect (significant heterogeneity in study design/patient selection)	
	Inhaled IFN- β treatment	14-day treatment with inhaled IFN- β within 24 hours of developing cold symptoms ¹³⁶	Adults Previous viral attack and ≥1 viral attack in last 24 months, n=147	No effect on 1 ^o outcome (ACQ). Morning PEFR ↑ in treatment group and both measures ↑ in severe asthma subgroup	

ACQ, Asthma Control Questionnaire; ED, emergency department; ICS, inhaled corticosteroid; IFN- β , interferon β ; OCS, oral corticosteroid; PEFR, peak expiratory flow rate; RCT, randomised controlled trial; SABA, short-acting β -agonist; SMART, steroid in maintenance and reliever therapy.

increased bronchodilators are recommended for all severe attacks. Peak flow is the only marker of airway obstruction regularly measured, although this may not be a sensitive marker of patient-reported attacks,⁵⁴ and is often not measured by patients despite symptom worsening.⁸⁴ The use of more sophisticated effort-independent measures of obstruction such as focused oscillometry in attacks requires evaluation. The most accessible marker of airway inflammation acutely, the blood eosinophil count, is useful in predicting steroid responsiveness in stable disease but its significance in acute asthma is unknown. Other potential biomarkers such as exhaled nitric oxide⁸⁵ and volatile organic compounds⁸⁶ which are being actively explored in the management of stable asthma may also have a role in the treatment of acute attacks. The ability of near patient testing devices based on rapid PCR techniques to detect common respiratory viruses is improving and may prove a valid strategy for appropriately directed antiviral therapy.⁸⁷ An approach based on detection of blood gene expression signatures⁸⁸ could also prove efficacious in distinguishing between bacterial, viral and non-infectious causes of exacerbations to guide acute treatment.

SUMMARY

In summary, asthma attacks are critically important events linked to excessive morbidity and mortality. There are many challenges to be overcome to improve outcomes relating to attacks. These include a limited and subjective definition of these events and a lack of understanding about their underlying complexity which have hindered efforts to stratify patient attack risk and mitigate this risk by targeting appropriate preventative treatment. Acutely, asthma attacks are all managed in the same way despite questionable efficacy of current interventions in some patient groups.

We believe that there is convincing evidence of heterogeneity in acute asthma attacks as there is in stable asthma and that over the next decade we will see improved treatment of asthma attacks, moving away from high-dose corticosteroids for all towards a phenotype-directed personalised treatment approach which has transformed the management of severe stable asthma in recent years.

Further studies are required in this area to: (1) explore and validate more sensitive and specific criteria to define attacks with the aim of producing standardised objective definitions of attack, (2) further

elucidate the mechanisms/characteristics of attacks in well-phenotyped patients across the spectrum of asthma severity and in those taking biological treatment, including superior characterisation and quantification of allergic, environmental, viral and bacterial (through DNA-based techniques) exposures, (3) identify robust, easily measured markers of impending attack to allow timely intervention to abort these and (4) ultimately investigate selective targeting of acute and preventative treatment for attack based on improved understanding and detection of attack phenotypes.

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REFERENCES

- Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;14:113.
- Office for National Statistics (ONS). All data related to national deaths and populations, 2017.
- Bahaduri K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
- O'Byrne PM, Pedersen S, Lamm CJ, et al. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;179:19–24.
- Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:28–34.
- Global Initiative for Asthma. Global strategy for asthma management and prevention 2019. Available: <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf>
- Reddel HK, Taylor DR, Bateman ED, et al. An official American thoracic society/ European respiratory society statement: asthma control and exacerbations. *Am J Respir Crit Care Med* 2009;180:59–99.
- Virchow JC, Bader V, de Blay F, et al. Defining moderate asthma exacerbations in clinical trials based on ATS/ERS joint statement. *Respir Med* 2015;109:547–56.
- Bourdin A, Bjerner L, Brightling C, et al. ERS/EAAACI statement on severe exacerbations in asthma in adults: facts, priorities and key research questions. *Eur Respir J* 2019;54:1900900.
- Fuhlbrigge AL, Bengtsson T, Peterson S, et al. A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. *Lancet Respir Med* 2017;5:577–90.
- Fuhlbrigge AL, Harrison TW, Fageris M, et al. An investigation of geographic influence on Complex, a surrogate endpoint for severe asthma exacerbations. *A1298-A1. American Thoracic Society International Conference Abstracts: American Thoracic Society 2019a*.
- Suruki RJ, Daugherty JB, Boufadi N, et al. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med* 2017;17:74.
- Schoot CJ, Palmer T, Peary J, et al. Exacerbation patterns in adults with asthma in England: a population based study. *American Journal of Respiratory and Critical Care Medicine* 2018.
- Blam M, McClellan LM, Kim M, et al. Asthma exacerbation rates in adults are unchanged over a 5-year period despite high-intensity therapy. *J Allergy Clin Immunol* 2014;25:70–4.
- Miller MK, Lee JH, Miller DP, et al. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med* 2007;101:481–9.
- Yeo A, Puaiah S, Lim HF, et al. A national audit of severe life-threatening asthma in Singapore. *European Respiratory Journal* 2018;52:PA3957.
- Sato R, Tomita K, Sano H, et al. The strategy for predicting future exacerbation of asthma using a combination of the asthma control test and lung function test. *J Asthma* 2009;46:677–82.
- Morjaria JB, Rigby AS, Morice AH. Asthma phenotypes: do cough and wheeze predict exacerbations in persistent asthma? *European Respiratory Journal* 2010;35:1701366.
- Frey U, Brodbeck T, Majumdar A, et al. Risk of severe asthma episodes predicted from fluctuation analysis of airway function. *Nature* 2005;438:667–70.
- Thamrin C, Zindl J, Nydegger R, et al. Predicting future risk of asthma exacerbations using individual conditional probabilities. *J Allergy Clin Immunol* 2011;127:494–502.
- Pavord ID, Beasley R, Agosti A, et al. After asthma: redefining airways diseases. *The Lancet* 2018;391:350–400.
- Loymans RJB, Honkoop PJ, Termeer EH, et al. Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable predictive model. *Thorax* 2017;72:1838–46.
- Bateman ED, Buhl R, O'Byrne PM, et al. Development and validation of a novel risk score for asthma exacerbations: the risk score for exacerbations. *J Allergy Clin Immunol* 2015;135:1457–64.
- Loymans RJB, Debray TPA, Honkoop PJ, et al. Exacerbations in adults with asthma: a systematic review and external validation of prediction models. *J Allergy Clin Immunol Pract* 2018;6:1942–52.
- Kang H-R, Song HJ, Nam JH, et al. Risk factors of asthma exacerbation based on asthma severity: a nationwide population-based observational study in South Korea. *BMJ Open* 2018;8:e020825.
- Semprini R, Williams M, Semprini A, et al. Type 2 biomarkers and prediction of future exacerbations and lung function decline in adult asthma. *J Allergy Clin Immunol* 2018;6:1982–8.
- Kupczyk M, ten Brinke A, Sterk PJ, et al. Frequent exacerbations – a distinct phenotype of severe asthma. *Clin Exp Allergy* 2014;44:212–21.
- Fricker M, Gibson PG, Powell H, et al. A sputum 6-gene signature predicts future exacerbations of poorly controlled asthma. *J Allergy Clin Immunol* 2019;144:51–60.
- Gonen S, Umar I, Burke D, et al. Airway impedance entropy and exacerbations in severe asthma. *Eur Respir J* 2012;40:1156–63.
- Teach SJ, Gill MA, Toggas A, et al. Preseasonal treatment with eitheromalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136:1476–85.
- Candet JC, Casale TB. New insights into the utility ofomalizumab. *Journal of Allergy and Clinical Immunology* 2019;143:923–6.
- Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. *J Allergy Clin Immunol* 2017;15:918–27.
- Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol* 2010;125:1178–87. quiz 88–9.
- Gern JE. Virus/Allergen interaction in asthma exacerbation. *Ann Am Thorac Soc* 2015;12:S137–43.
- Edwards MR, Strong K, Cameron A, et al. Viral infections in allergy and immunology: how allergic inflammation influences viral infections and illness. *J Allergy Clin Immunol* 2017;140:909–20.
- Patel DA, You Y, Huang G, et al. Interferon response and respiratory virus control are preserved in bronchial epithelial cells in asthma. *J Allergy Clin Immunol* 2014;134:1402–12.
- Sheehan WJ, Phipatanakul W. Indoor allergen exposure and asthma outcomes. *Curr Opin Pediatr* 2016;28:772–7.
- Erbas B, Jazayeri M, Lambert KA, et al. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: a systematic review and meta-analysis. *Allergy* 2018;73:1632–41.
- Cakmak S, Dales RE, Coates F. Does air pollution increase the effect of aeroallergens on hospitalization for asthma? *J Allergy Clin Immunol* 2012;128:228–31.
- Marks GB et al. Thunderstorm outflows preceding epidemics of asthma during spring and summer. *Thorax* 2001;56:468–71.
- Johnston SL, Martin RJ. Chlamydia pneumoniae and Mycoplasma pneumoniae: a role in asthma pathogenesis? *Am J Respir Crit Care Med* 2002;165:1078–89.
- Yoshi Y, Shimizu K, Morozumi M, et al. Detection of pathogens by real-time PCR in adult patients with acute exacerbation of bronchial asthma. *BMC Pulm Med* 2017;17:150.
- Kim C-K, Callaway Z, Gern JE. Viral infections and associated factors that promote acute exacerbations of asthma. *Allergy Asthma Immunol Res* 2018;10:12–17.
- Oliver BGG, Lim S, Wark P, et al. Rhinovirus exposure impairs immune responses to bacterial products in human alveolar macrophages. *Thorax* 2008;63:519–25.
- Edwards MR, Saglani S, Schwarz J, et al. Addressing unmet needs in understanding asthma mechanisms. *Eur Respir J* 2017;49:1602448.
- Barr RG, Woodruff PG, Clark S, et al. Sudden-onset asthma exacerbations: clinical features, response to therapy, and 2-week follow-up. multicenter airway research collaboration (mARC) Investigators. *Eur Respir J* 2000;15:266.
- Rodrigo GJ, Rodrigo C. Rapid-Onset asthma attack: a prospective cohort study about characteristics and response to emergency department treatment. *Chest* 2000;118:1547–52.
- Pérez V, Serrano J, Picado C, et al. Frequency and clinical characteristics of rapid-onset fatal and near-fatal asthma. *Eur Respir J* 2002;19:846–52.
- Ramath RV, Clark S, Camargo CA. Multicenter study of clinical features of sudden-onset versus slower-onset asthma exacerbations requiring hospitalization. *Respir Care* 2007;52:1013.
- Hyun RC, Travis WD, Hanna E, et al. Slow-onset asthma deaths have more eosinophils and health care utilization than rapid-onset deaths. *Respir Med* 2008;102:1819–26.
- James AL, Elliot JC, Abramson MJ, et al. Time to death, airway wall inflammation and remodelling in fatal asthma. *Eur Respir J* 2005;26:429–34.
- Sur S, Crotty TB, Kephart GM, et al. Sudden-onset asthma: A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *Ann Rev Respir Dis* 1993;148:173–9.
- Wasserman J-B, Schaller M-D, Feil F, et al. Sudden Asphyctic asthma: a distinct entity? *Ann Rev Respir Dis* 1990;142:108–11.
- Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma. *Am J Respir Crit Care Med* 1999;160:594–9.
- Picher J, Patel M, Pritchard A, et al. Beta-Agonist overuse and delay in obtaining medical review in high risk asthma: a secondary analysis of data from a randomised controlled trial. *npj Primary Care Respiratory Medicine* 2017;27:33.
- Patel M, Pilcher J, Hancox RJ, et al. The use of β_2 -agonist therapy before Hospital admission for severe asthma exacerbations: a post-hoc analysis. *npj Prim Care Resp Med* 2015;25:14099.
- Chan-Yeung M, Chang JH, Manfreda J, et al. Changes in peak flow, symptom score, and the use of medications during acute exacerbations of asthma. *Am J Respir Crit Care Med* 1996;154:889–93.
- Reddel H, Wain S, Marks G, et al. Differences between asthma exacerbations and poor asthma control. *Lancet* 1999;353:364–9.
- Bardin PG, Fraenkel DJ, Sanderson G, et al. Peak expiratory flow changes during experimental rhinovirus infection. *Eur Respir J* 2000;16:980–5.
- Jackson DJ, Makrinioti H, Rana BM, et al. IL-33–Dependent Type 2 Inflammation during Rhinovirus-induced Asthma Exacerbations In Vivo. *Am J Respir Crit Care Med* 2014;190:1373–82.
- Hasegawa K, Stoll SJ, Ahn J, et al. Prevalence of eosinophilia in hospitalized patients with asthma exacerbation. *Respir Med* 2015;109:1230–2.
- Qiu R, Xie J, Chung KF, et al. Asthma phenotypes defined from parameters obtained during recovery from a Hospital-Treated exacerbation. *J Allergy Clin Immunol* 2018;6:1960–7.
- Qiu Y, Zhu J, Bandi V, et al. Bronchial mucosal inflammation and upregulation of CXCR chemotactic receptors in severe exacerbations of asthma. *Thorax* 2007;62:475–82.
- Lamblin C, Gosset P, Tillie-Leblond I, et al. Bronchial neutrophilia in patients with noninfectious status asthmaticus. *Am J Respir Crit Care Med* 1998;157:394–402.
- Wang F, He XY, Bajnes KJ, et al. Different inflammatory phenotypes in adults and children with acute asthma. *European Respiratory Journal* 2011;38:567–74.
- Pizzichini MM, Pizzichini E, Clelland L, et al. Sputum in severe exacerbations of asthma: kinetics of inflammatory indices after prednisone treatment. *Am J Respir Crit Care Med* 1997;155:1501–8.
- Mannes E, Nieves A, Loree A-M, et al. T-Cell activation during exacerbations: a longitudinal study in refractory asthma. *Allergy* 2008;63:1202–10.
- Bjornsdottir US, Holgate ST, Reddy PS, et al. Pathways activated during human asthma exacerbation as revealed by gene expression patterns in blood. *PLoS One* 2011;6:e21902.
- Bjornsdottir US, Pizzichini MM, Cook RJ, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;27:383–94.
- Gibson PG, Wong BJQ, Hepperle MJE, et al. A research method to induce and examine a mild exacerbation of asthma by withdrawal of inhaled corticosteroid. *Clin Exp Allergy* 1992;22:525–32.
- int Veen JC, Smiths HH, Hiemstra PS, et al. Lung function and sputum characteristics of patients with severe asthma during an induced exacerbation by double-blind steroid withdrawal. *Am J Respir Crit Care Med* 1999;160:93–9.
- Pizzichini MM, Pizzichini E, Clelland L, et al. Prednisone-Dependent asthma: inflammatory indices in induced sputum. *Eur Respir J* 1999;13:15–21.
- Zhu J, Messing SD, Qiu Y, et al. Airway inflammation and illness severity in response to experimental rhinovirus infection in asthma. *Chest* 2014;145:1219–29.
- Jarjour NN, Gem JE, Kelly EAB, et al. The effect of an experimental rhinovirus 16 infection on bronchial lavage neutrophils. *Journal of Allergy and Clinical Immunology* 2000;105:1169–77.
- Messing SD, Lanza-Silva Y, Mallat P, et al. Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci U S A* 2008;105:13362–7.
- Fraenkel DJ, Bardin PG, Sanderson G, et al. Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. *Am J Respir Crit Care Med* 1995;151:879–86.
- Beale J, Jayaraman A, Jackson DJ, et al. Rhinovirus-Induced IL-25 in asthma exacerbation drives type 2 immunity and allergic pulmonary inflammation. *Sci Transl Med* 2014;6:256ra134–256.
- Han M, Rajput C, Hong JY, et al. The innate cytokines IL-25, IL-33, and TSLP cooperate in the induction of type 2 innate lymphoid cell expansion and mucous metaplasia in rhinovirus-infected immature mice. *J Immunol* 2017;199:1308–18.
- Denlinger LC, Sorness RL, Lee W-M, et al. Lower airway rhinovirus burden and the seasonal risk of asthma exacerbation. *Am J Respir Crit Care Med* 2011;184:1007–14.
- Wark PAB, Johnston SL, Moric I, et al. Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. *Eur Respir J* 2002;19:68–75.
- Bjornsdottir A, Laing JA, Bader V, et al. Clinical characteristics of eosinophilic asthma exacerbations. *Respirology* 2017;22:295–300.
- Bjornsdottir A, Laing JA, Poulsen N, et al. Characteristics associated with clinical severity and inflammatory phenotype of naturally occurring virus-induced exacerbations of asthma in adults. *Respir Med* 2017;123:34–41.
- McDonald VM, Hiles SA, Godbout K, et al. Treatable traits can be identified in a severe asthma registry and predict future exacerbations. *Respirology* 2019;24:37–47.
- McKever T, Mortimer K, Wilson A, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med* 2018;378:902–10.
- Harrison T, Whelan G, Fageris M, et al. STIFLE: an exploratory longitudinal study to characterize daily changes and relationships in airway inflammation, symptoms, lung function, and relieve use in adult asthma patients. A32 asthma: clinical studies II. American Thoracic Society International Conference Abstracts: American Thoracic Society 2019:A1308.
- Wilde M, Cordell R, Richardson M, et al. Optimising the discovery of Breath-Based biomarkers for phenotyping acute exacerbations of asthma and COPD. A31 asthma: clinical studies I. American Thoracic Society International Conference Abstracts: American Thoracic Society 2019:A1292.
- Bjornsdottir US, Mills S, Ewings S, et al. Impact of point-of-care testing for respiratory viruses on antibiotic use in adults with exacerbation of airways disease. *J Infect* 2019.
- Lyden EC, Bullard C, Ajdin M, et al. A host gene expression approach for identifying triggers of asthma exacerbations. *PLoS One* 2019;14:e0214871.
- Blyden DJ, Price DB, Pizzichini E, et al. Identifying risk of future asthma attacks using UK medical record data: a respiratory effectiveness group initiative. *J Allergy Clin Immunol* 2017;5:1015–24.
- Patel M, Pilcher J, Reddel HK, et al. Predictors of severe exacerbations, poor asthma control, and β_2 -Agonist overuse for patients with asthma. *J Allergy Clin Immunol* 2014;2:751–8. 91 Chippis BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. *J Allergy Clin Immunol* 2012;130:332–42.
- Bateman ED, Reddel HK, Eriksson G, et al. Overall asthma control: the relationship between current control and future risk. *J Allergy Clin Immunol* 2010;125:600–8.
- Engelkes M, Janssens HM, de Jongste JC, et al. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015;45:396–407.
- Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011;105:930–8.
- Price D, Wilson AM, Chisholm A, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy* 2016;9:1–12.
- Denlinger LC, Phillips BR, Ramrattam S, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med* 2017;195:302–13.
- ten Brinke A, Sterk PJ, Masclee AAM, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005;26:812–8.
- Fitzpatrick S, Joks R, Silverberg JL. Obesity is associated with increased asthma severity and exacerbations, and increased serum immunoglobulin E in inner-city adults. *Clin Exp Allergy* 2012;42:747–59.
- Sin DD, Man J, Sharpe H, et al. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *Jama* 2004;292:367–76.
- John Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715–21.
- Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev* 2014;1:Cd003559.
- Mitchell PD, El-Gamali AI, O'Byrne PM. Anti-IgE and biologic approaches for the treatment of asthma. *Handb Exp Pharmacol* 2017;237:131–52.
- Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects ofomalizumab in allergic asthma: an analysis of biomarkers in the extra study. *Am J Respir Crit Care Med* 2013;187:804–11.
- Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from Prospero, a prospective real-world study. *J Allergy Clin Immunol Pract* 2017;15:6–64.
- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651–9.
- Shrimanker R, Pavord ID, Yancey S, et al. Exacerbations of severe asthma in patients treated with mepolizumab. *Eur Respir J* 2018;52:1801127.
- Sidagolli P, Perero VS, Bal SM, van de Pol MA, et al. Anti-IL5 in mild asthma alters rhinovirus-induced macrophage, B cell and neutrophil responses in a placebo-controlled, double-blind study. *Am J Respir Crit Care Med* 2018.
- Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016;4:549–56.
- Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486–96.
- 101 Sobieraj DM, Baker WL, Nguyen E, et al. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: a systematic review and meta-analysis. *JAMA* 2018;319:1473–84.
- 111 Chari VM, McIvor RA. Tiotropium for the treatment of asthma: patient selection and perspectives. *Cann Respir J* 2018;2018:1–10.
- 112 Loymans RJB, Gemperli A, Cohen J, et al. Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis. *BMJ* 2014;348:g3009.
- 113 Kelly MM, O'Connor TM, Leigh R, et al. Effects of budesonide and formoterol on allergen-induced airway responses, inflammation, and airway remodeling in asthma. *J Allergy Clin Immunol* 2010;125:349–56.
- 114 Zhang H, Jia JC, Lv J, et al. Montelukast for prevention and treatment of asthma exacerbations in adults: systematic review and meta-analysis. *Allergy Asthma Proc* 2014;35:278–87.
- 115 Johnston NW, Mandhane PJ, Dai J, et al. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007;120:702–12.
- 116 Brusselle GG, Vandecasteele C, Jorde P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013;68:322–9.
- 117 Gibson PG, Yang LA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:659–68.
- 118 Gibson PG, Yang LA, Upham JW, et al. Efficacy of azithromycin in severe asthma from the AMAZES randomised trial. *ERJ Open Res* 2019;5:00056-2019–19.
- 119 Gibson PG, Powell H, Wilson A, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database of Systematic Reviews* 2002,3.
- 120 Contreras J, Barnes RJ, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med* 2017;377:936–46.
- 121 Lee H-C, Hensley MB, Loo Y-M, et al. Thymic stromal lymphopoietin is induced by respiratory syncytial virus-infected airway epithelial cells and promotes a type 2 response to infection. *J Allergy Clin Immunol* 2013;130:1187–96.
- 122 Gonen S, Berar R, Singapur A, et al. Fevipitant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled study. *Lancet Respir Med* 2016;4:699–707.
- 123 Barnes N, Pavord J, Chuchalin A, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OCO00459 in moderate persistent asthma. *Clin Exp Allergy* 2012;42:38–48.
- 124 Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest* 1998;113:593–8.
- 125 Kirkland SW, Vandenberghe C, Voaklander B, et al. Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma. *Cochrane Database Syst Rev* 2017;1:Cd001284.
- 126 Kew KM, Kirshuk L, Mitchell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database of Systematic Reviews* 2015,4.
- 127 Fritz G, Hahn J, Becker A, Sayer SM, et al. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004;59:550–4.
- 128 Harrison TW, Osborne J, Newton S, et al. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet* 2004;363:271–5.
- 129 Jackson DJ, Bacharier LB, Mauger DT, et al. Quinupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *N Engl J Med* 2018;378:891–901.
- 130 Kaiser SV, Huynh T, Bacharier LB, et al. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. *Pediatrics* 2016;137:e20154496.
- 131 Reddel HK, Jenkins C, Quirce S, et al. Effect of different asthma treatments on risk of cold-related exacerbations. *Eur Respir J* 2011;38:584–93.
- 132 Kearns N, Majers I, Harper J, et al. Inhaled corticosteroids in acute asthma: a systemic review and meta-analysis. *J Allergy Clin Immunol Pract* 2008;6:605–17.
- 133 Rowe BH, Spooner C, Ducharme FM, et al. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001;1:Cd001278.
- 134 Rowe BH, Spooner C, Ducharme F, et al. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database of Systematic Reviews* 2007,324.
- 135 Normansell R, Sayer B, Waterson S, et al. Antibiotics for exacerbations of asthma. *Cochrane Database Syst Rev* 2018;6:Cd002741.
- 136 Djukanovic R, Harrison T, Johnston SL, et al. The effect of inhaled IFN- γ on worsening of asthma symptoms caused by viral infections. A randomized trial. *Am J Respir Crit Care Med* 2014;190:145–54.

ARTIGO ORIGINAL INVESTIGAÇÃO

Associação da gravidade da asma e desempenho escolar aos 6-7 anos numa coorte de nascimento: estudo de base populacional com ligação de registos

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RESUMO

Contexto Existe uma investigação contraditória sobre a associação entre a asma e o insucesso escolar que pode dever-se às definições de asma. O nosso estudo cria sete categorias da atual asma crónica e aguda para investigar se existe uma associação entre o insucesso escolar aos 6-7 anos e qual o papel das infeções respiratórias e do absentismo escolar.

Métodos Este estudo utilizou uma coorte de nascimento transversal, eletrónica e de base populacional entre 1998-2005 no País de Gales, Reino Unido, utilizando conjuntos de dados administrativos em matéria de saúde e educação. As atuais categorias de asma ou pieira foram desenvolvidas utilizando diretrizes de gestão clínica em dados de clínica geral (CG). A asma aguda teve por base as admissões hospitalares e as infeções respiratórias tiveram por base o número de consultas com um clínico geral desde o nascimento até aos 6-7 anos de idade. Aplicámos os modelos de regressão logística multinível agrupados por escolas para verificar se a asma ou pieira estavam associadas ao não cumprimento do nível esperado nas avaliações dos professores na *Key Stage 1* (KS1), ajustado para dados sociodemográficos, doenças perinatais, outras doenças respiratórias e características escolares. Testámos se o absentismo escolar constituía um mediador nesta relação, utilizando o método da diferença.

Resultados Existiam 85 906 crianças nesta coorte representativa da população com 7 anos de seguimento. Na regressão logística multinível ajustada, apenas a admissão hospitalar por asma foi associada ao aumento do risco de incumprimento do nível esperado em KS1 (OR ajustado 1,14 95% IC (1,02 a 1,27)). As consultas de CG para infeção do trato respiratório inferior (ITRI) continuaram a ser um preditor independente para o incumprimento do nível de educação esperado. O absentismo escolar foi um potencial mediador da associação entre a admissão hospitalar e o sucesso escolar.

Conclusões Os médicos e educadores precisam de estar alertados para o facto de que as crianças hospitalizadas por asma ou pieira, ou por infeções repetidas de asma, podem necessitar de apoio educacional adicional para o cumprimento dos objetivos educacionais.

INTRODUCTION

Asthma is a common childhood condition, with prevalence of current asthma (symptoms within the last year) at age 7 years estimated to be 12% in the UK,¹ similar to Australia² and the USA.³ Cumulative prevalence of wheeze was found to be between 15% and 26% during the first 7 years of childhood in the UK,⁴ with current wheeze at age 6-7 years from 7% in the Indian subcontinent to 21% in English language centres (UK, Australia, Canada, New Zealand) and Oceania (22%).⁵ Healthcare and societal burden of asthma in the UK was thought to be in excess of £1.1 billion in 2011-2012.⁶ Clinicians mostly follow asthma management guidelines^{7,8} that advise step changes in medication or a hospital admittance by age of the child.

Key messages

What is the key question?

► Is asthma or wheeze severity during the first six years of life associated with educational attainment at age 6-7 years, should we consider the influence of respiratory infections and does school absence explain the relationship?

What is the bottom line?

► After multivariable adjustment, asthma severity has no association with education outcomes at age 6-7 years, but inpatient hospital admissions for acute asthma or wheeze were associated with increased risk for not attaining the expected level of education for children.

Lower respiratory tract infections were also an independent predictor for not attaining the expected level in education. School absence was found to potentially explain the association between acute asthma and lower educational attainment.

Why read on?

► This is the first study to consider interactions between asthma and respiratory infections coded in general practice consultations and hospital admissions on educational attainment.

The cohort contained 85 000 children and rich covariate information, allowing us to adjust for numerous factors including sociodemographics, birth and school characteristics in modelling the association between asthma and education outcome.

Decisions to step up or step down in the management plan are based on assessment usually after any hospital admission for acute exacerbation and include consideration of previous hospital admission, Paediatric Intensive Care Unit (PICU) admission, recent steroids, psychological and family issues, compliance/adherence issues, response to initial treatment, distance from home and family preference. Chronic asthma is managed using regular reviews, and guidelines differ for recommendations of a step change due to frequency of exacerbations either to enable no acute exacerbations or when more than two to three exacerbations occur in a year. These guidelines for asthma include school attendance but do not include evidence on the impact of hospital admissions or the burden of co-occurring respiratory infections on educational outcomes.

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Asthma aetiology is multifactorial, diagnosed by a combination of symptoms of inflammation in the airways with reversible airway narrowing and airway hyper-responsiveness. Acute asthma exacerbations present as the onset of wheeze and respiratory distress. In young children, clinicians often diagnose viral-induced wheeze but do not diagnose asthma, as symptoms may resolve as the child grows older. Upper respiratory tract infections (URTIs) are also common during childhood, and found to occur between three and eight times a year in primary or preschool children.^{9,10} Children with asthma may experience more severe symptoms when they acquire a respiratory infection.¹¹

Children with asthma who suffer frequent exacerbations that may require intervention by a general practitioner or a hospital stay may miss school days, resulting in lower educational attainment compared with their peers, but evidence about asthma between age 5 and 9 years is mixed. Two studies in the USA and UK have reported that well-managed asthma had little impact on educational attainment^{12,13} or for repeating a school year,^{14,15} although others showed those with asthma had lower educational attainment^{16,17} compared with those without. Three studies examined severity of asthma with conflicting outcomes: one study in New Zealand showed no difference in educational outcomes,¹⁷ two studies associated higher severity with poorer school readiness¹⁸ or educational attainment.¹⁹ These conflicting results may be due to different definitions of asthma, reliance on parental reporting, inclusion of older children and teenagers, and not adjusting for important confounders such as birth characteristics, other respiratory illness including common infections or school factors in statistical analyses.

This study investigates whether or not asthma severity is associated with educational attainment using a teacher-based assessment at age 7 years (Key Stage 1, KS1). Our study adds to the evidence because it uses a large population-based cohort, enabling us to derive measures of current acute asthma and categories of chronic asthma severity that closely match current asthma management guidelines using general practice (GP) diagnoses and prescriptions, and hospital admissions administrative data. We explored whether respiratory infections may act as an additional exposure and interact with the association of asthma on educational attainment. We explored the role of school absences where data were available (the school year when KS1 was taken where assessment usually starts in the final 2½ months) in the relationship between asthma severity and educational outcome. Our analysis took account of multiple important confounders (perinatal factors and social deprivation) and school factors not previously seen modelled together in other studies for this specific age group.

METHODS

Study design and setting

We used a population-based cross-sectional electronic cohort of all children born in Wales, from 1 January 1998 to 31 August 2005. This was a preplanned record-linkage study consistent with the broad aims of the cohort, with linkage to prospectively collected health and education administrative data. Data were extracted for asthma, wheeze and other respiratory diagnosis from GP or inpatient hospital admissions data. Children were followed up from birth to age 6–7 years, to their first teacher-based educational assessment at KS1, through record linkage between education and health routine datasets.

Data sources and participants

We analysed deidentified data in the Secure Anonymized Information Linkage (SAIL) databank, UK,^{20,21} using the Wales Electronic Cohort for Children (WECC),²² developed from five health and demographic national datasets detailed in online supplemental table S1. WECC includes all children living in Wales during 1990–2012 in the Wales Demographic Service (WDS), from registration with a GP in the National Health Service (NHS). We record-linked these children to the General Practice Database (GPD), containing all contacts with general medical practitioners (including nurse appointments), and to national educational databases through NHS number (health datasets only), name, date of birth,

gender, and phonetic and soundex version of names (online supplemental table S1).

Children were excluded if they were not born in Wales (as these children had high levels of missing data for birth characteristics), born before 1 January 1998 (as electronic GP and hospital inpatient admissions data were not available from the data sources before this date) or after 31 August 2005 (as they would not have sufficient follow-up to age 6–7 years). Further exclusions were children who died or moved out of Wales before age 7 years, who did not attend a local education authority school, did not take KS1 at the normal age or where the child's GP practice had not signed up to SAIL (figure 1). At the time of data extraction, the GPD in the SAIL databank had over 40% of the 474 practices in Wales signed up, and over 1.9 million people.

Outcome

The main outcome was attainment of the expected educational level (yes/no), in compulsory assessment in Wales at age 6–7 years (KS1), normally taught between age 5 and 7 years.²³ KS1 is a teacher assessment of a language, mathematics and science with overall level awarded between 0 and 4, where below level 2 constitutes not attaining the expected level at KS1. Children who were disapplied (not taking the subject), not awarded the level, unable to provide an assessment or working towards the assessment level were coded as did not attain the expected level at KS1 in this study, in agreement with definitions by the Welsh Department of Education.

Exposures

Current chronic asthma severity was derived using data on diagnoses and prescriptions, and acute asthma from inpatient hospital admissions. Asthma or wheeze was ascertained in GP data (using a set of previously published Read codes in the GPD²⁴) or International Classification of Diseases 10th Revision (ICD10) codes J45–46, R06.² in the first coding position of any inpatient hospital admission (including hospital transfers) between birth and age 7 years. We developed two algorithms to derive categorical variables that describe current chronic asthma severity: one excluded wheeze-only diagnoses (called the asthma severity algorithm), while the second, a broader algorithm included wheeze (called the wheeze severity algorithm). Chronic asthma severity was recorded for each year of the child's life, aligned to five levels of asthma management (based partly on yearly prescriptions) described in the National Heart, Lung and Blood Institute (NHLBI) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007 (USA).⁷ An additional category was created where only a diagnosis was recorded. These guidelines were compared with current UK assessment and stepwise treatment guidelines for the clinical management of asthma^{8,25} to create an algorithm that met both criteria, as described in table 1 (coding lists in online supplemental tables 3–6; online supplemental figure S1). These two algorithms enabled us to compare analyses based on definitive diagnoses of asthma (from ongoing prescriptions of inhaled corticosteroid or preventer medication, or tests such as spirometry—usually only achievable from age 5 years) with those in a broader definition, that is, children diagnosed with either wheeze or asthma.

For the main analysis, we chose the most severe category of asthma from the yearly calculations as exposure status for each child between birth and age 7 years for simplicity, and in further analyses, split status by age less than 2 years, 2–<5 years, 5–<7 years to closely match the guidelines and age when KS1 is taught. We labelled the current chronic asthma severity categories as 'none', 'diagnosis only', 'intermittent bronchodilator', 'persistent mild', 'persistent moderate' and 'persistent severe' to match guideline categories (table 1).

Two further variables were created for acute asthma or wheeze using inpatient hospital admissions in the Patient Episode Database Wales dataset from birth to KS1. Acute asthma was defined with ICD10 codes J45–46, and acute asthma or wheeze included an additional code R06.² for wheezing. Where children did not have a previous diagnosis, the initial hospital admission was excluded from these variables to allow for the possibility that prescribed medication following this admission may control symptoms.

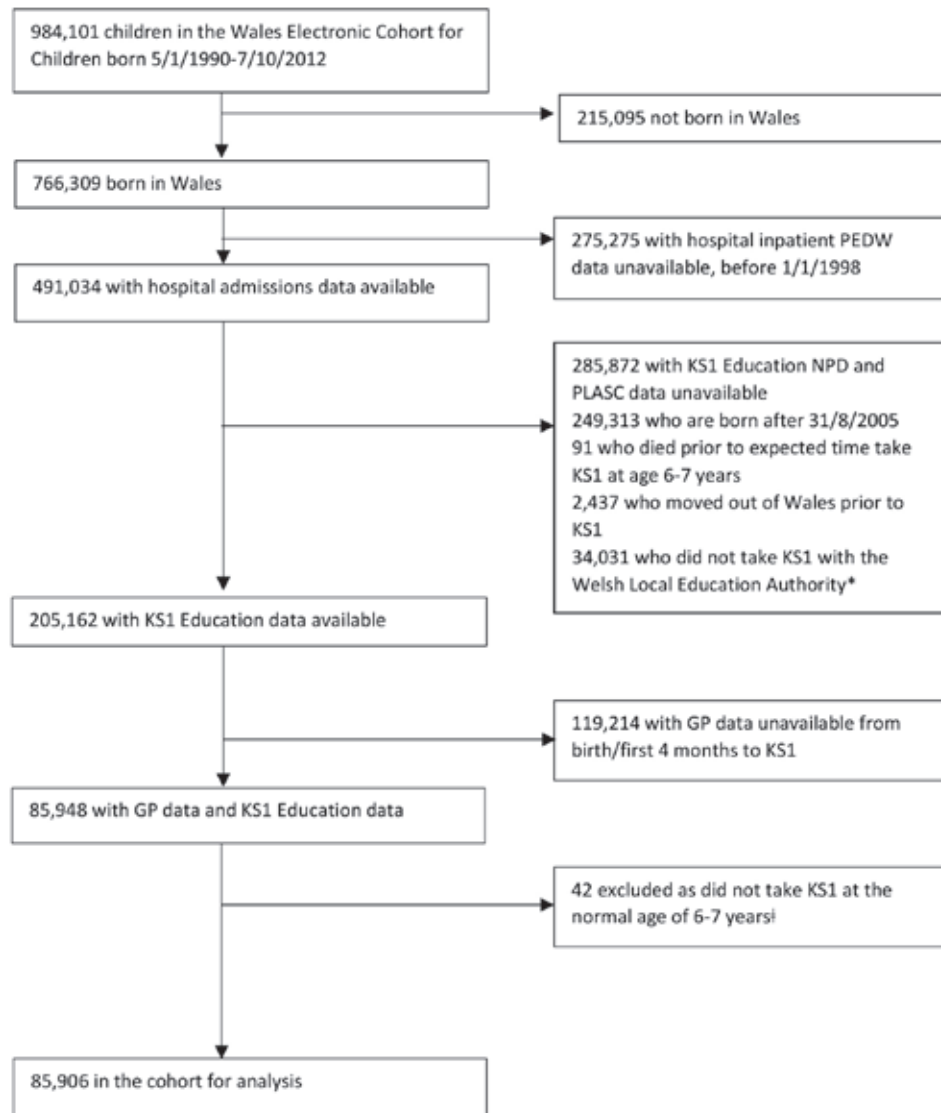


Figure 1 Anonymised participant selection. KS1, Key Stage 1; NPD, National Pupil Database; PEDW, Patient Episode Database Wales; PLASC, Pupil Level Annual School Census. *Private schools, severely disabled children who are not catered for by special educational needs provision in the LEA school system, those outside administrative systems, for example, travellers. †To adhere to no overlap between exposure and outcome time windows. LEA, Local Education Authority.

Respiratory illness was ascertained from GP data and categorised as follows: lower respiratory tract infection (LRTI) including bronchiolitis when bronchitis was also coded, upper respiratory tract infection (URTI), influenza or pneumonia, bronchiolitis, chronic upper respiratory disease, chronic lower respiratory disease, croup and unspecified respiratory illness (online supplemental table S6). GP contacts between birth and KS1 were categorised by frequency, for example, 0, 1, 2 or more, to give a measure of burden of disease. For URTI, GP contacts were grouped into 0, 1–4, 5–6, 7+ as they were more common.

Potential confounders, covariates and effect modifiers

Birth characteristics were available from WECC for sex, gestation at birth, small for gestational birth (<10th centile) adjusted for gestation and sex, parity, major or minor congenital anomaly, maternal age, breast feeding recorded at birth or at 6–8 weeks, maternal cigarette smoking in first trimester, academic season of birth, and urban or rural dwelling at birth. Deprivation at birth was categorised into quintiles using Townsend deprivation scores of small area of residence Lower Super Output Area (LSOA) from the 2001 census. School datasets provided variables on school attended at KS1 assessment, school moves, year took KS1, percentage of absence from school (in the school year when KS1 was taken where assessment usually starts in the final 2½ months) and free school meals eligibility in the school year take KS1 (used as a proxy for deprivation level beyond birth).

Statistical analyses

The variable selection for analyses was informed by using a directed acyclic graph (figure 2).²⁶ Models were adjusted for school factors²⁷

because of the known association with variability in educational attainment. Special educational needs (SEN) provision at school was excluded from models due to its potential partial causal pathway between asthma and educational attainment (possibly occurring due to disruption to daily activities and missed school days), to investigate the impact of asthma rather than asthma after the effects of SEN provision. Likelihood ratio tests were used to investigate two-way interactions between chronic asthma severity and acute asthma, between these asthma variables and respiratory infections, sex or deprivation. We tested if absence from school was a mediator between asthma and educational attainment using the difference method.²⁸

Data were analysed using Stata V.13, hypothesis tests were two-sided and statistical significance was set at $p < 0.05$. The clinical significance of asthma may prevent a child from attaining the expected level at KS1, which may lead to reduced life chances in later education and employment, with little comparative cost to update pre-existing guidance for asthma for clinicians and educators. Multilevel logistic regression (QR decomposition) was used to obtain ORs for not attaining the expected level at KS1. To account for the possibility of unobserved shared factors leading to correlation of educational outcomes within schools, we used school-level random effects. We used Hosmer-Lemeshow goodness of model fit tests. Missing data were imputed using multiple imputations by chained equations of all the variables in the model²⁹ (five imputations), and no interpretable difference was found between imputed models and models with no-answer categories included.

Modelling was repeated for asthma and wheeze exposure split by age group for pairs of current chronic severity and acute variables to prevent possible effects of collinearity between different age groups.

Table 1 Description of asthma severity using administrative health datasets**Asthma or wheeze severity algorithms for this analysis (see coding in online supplemental tables 2–6)****Asthma severity algorithm**

Category	Coding description
None	No diagnosis of asthma between birth and KS1 (age 6–7 years)
Diagnosis only	Ever had an asthma diagnosis in either GP or hospital inpatient admissions data* between birth and age at KS1 (age 6–7 years)
Intermittent bronchodilator	>1 and ≤12 prescriptions of asthma bronchodilator including nebulisers in any 1 year of life, and ever had an asthma diagnosis in either GP or hospital inpatient admissions data* between birth and age at KS1 (age 6–7 years)
Persistent mild	Inhaled corticosteroid including nebulised or >12 bronchodilator prescriptions in any 1 year of life†, and ever had an asthma diagnosis in either GP or hospital inpatient admissions data* between birth and age at KS1 (age 6–7 years)
Persistent moderate	Inhaled corticosteroid including nebulised or >12 bronchodilator prescriptions in any 1 year of life†, and at least one prescription of a preventer medication (eg, long-acting beta agonists), and ever had an asthma diagnosis in either GP or hospital inpatient admissions data* between birth and age at KS1 (age 6–7 years)
Persistent severe	Asthma injection prescription, immunosuppressant therapy prescription or >3 oral corticosteroid prescriptions in any 1 year of life, and ever had an asthma diagnosis in either GP or hospital inpatient admissions data* between birth and age at KS1 (age 6–7 years)

Wheeze severity algorithm

Inpatient hospital diagnosis is the first diagnosis code of first consultant episode of each person's continuous stay in hospital including transfers.

†In this cohort, no child had >12 bronchodilator prescriptions in any 1 year of his/her life.
GP, general practice; KS1, Key Stage 1.

Sensitivity analysis was performed by including only one randomly selected child from each mother, to mitigate the potential for spuriously small SEs arising from correlation between outcomes for children born to the same mother.

RESULTS

There were 85906 children born in Wales between 1998 and 2005 with 7-year follow-up (figure 1). Baseline characteristics (table 2) were similar to those of the general population of Wales (online supplemental table S2). The prevalence of current chronic asthma

(using the asthma severity algorithm) in this cohort between birth and KS1 (age 6–7 years) was 12.5%, with 0.6% categorised as diagnosis only, 2.7% with intermittent bronchodilator, 7.3% persistent mild, 1.6% persistent moderate, 0.3% persistent severe, and for acute asthma 4.1% had an inpatient hospital admission (table 3). For the wider definition that included wheeze (wheeze severity algorithm), the prevalence was 21.4%, with noticeably higher proportions in categories of diagnosis only, intermittent bronchodilator, persistent mild, and acute asthma or wheeze inpatient hospital admissions (table 3). As expected for children with asthma, there were higher proportions in males, lower gestational age at birth, no breast feeding, maternal smoking in the first trimester, higher deprivation and urban compared with rural dwelling at birth (table 2).

Over 20% of children in each asthma severity category had an asthma inpatient hospital admission, with 69% of children in the persistent severe category admitted; patterns were relatively similar for asthma or wheeze severity (table 3). Multiple GP contacts for a child were found for respiratory infections, 11% of children had seven or more GP contacts for URTI and 8% had three or more GP contacts for LRTI.

Children with higher asthma severity had more GP contacts for LRTI, 17% of children with intermittent bronchodilator and 50% with persistent severe asthma had three or more GP contacts for LRTI, compared with 6% for those without a diagnosis of asthma (table 4). GP contacts for seven or more URTIs were 17% and 32% for the same asthma severity categories, compared with 10% in children without an asthma diagnosis. Similar proportions across the categories were seen for the broader wheeze severity algorithm (data not shown). Of the 8% of children with three or more LRTI GP contacts, 31% also had seven or more URTI GP contacts, and greater numbers were found in the most deprived quintile and those eligible for free school meals (data not shown).

Within the cohort, 14 935 (17%) children did not attain the expected level at KS1 (table 5), average age at assessment was 7 years 1 month (SD 3.5 months). Unadjusted analysis showed increased risk for all categories in the asthma severity algorithm for non-attainment of the expected level at KS1, the highest were diagnosis only (OR 1.58 95% CI 1.29 to 1.95), with similar size ORs for persistent severe and acute asthma from inpatient hospital admission. Over time, there were increased numbers of children who became diagnosed with persistent mild or persistent moderate asthma (online supplemental figure S2).

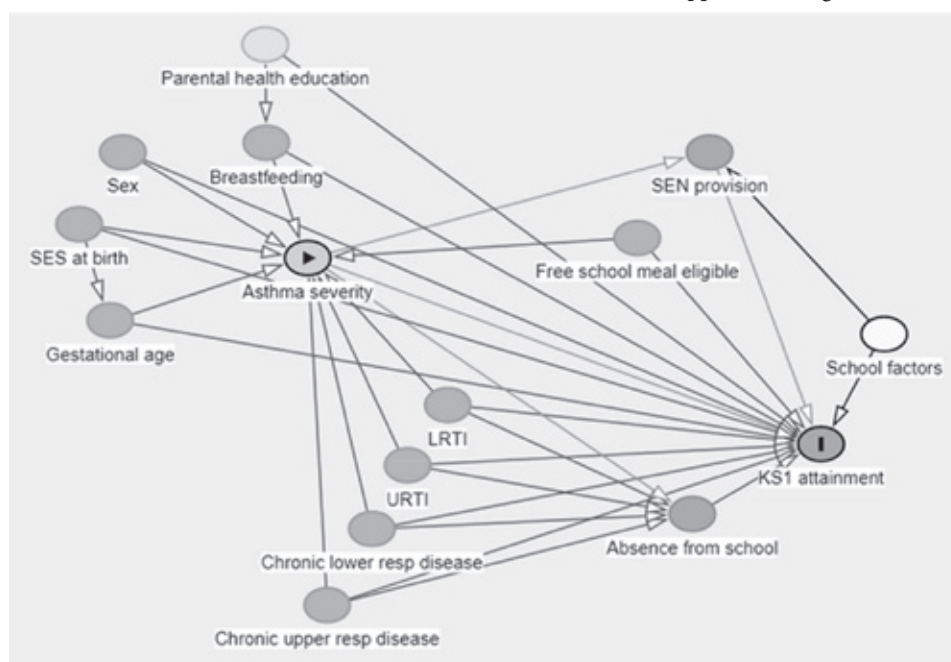


Figure 2 Directed acyclic graph causal diagram of asthma severity and Key Stage 1 attainment (at age 6–7 years). Chronic lower resp disease, chronic lower respiratory disease; chronic upper resp disease, chronic upper respiratory disease; KS1, Key Stage 1; LRTI, lower respiratory tract infection; SES, socioeconomic status (Townsend deprivation quintile, maternal cigarette smoking in the first trimester), gestational age (at birth), asthma severity (general practice contacts and hospital inpatient admissions), breastfeeding (at birth or 6–8 weeks); SEN, special educational needs, school factors (academic season of birth, school moves, urban or rural area at birth, schools level variable); URTI, upper respiratory tract infection. All theoretical causal relationships are drawn, where relationships may be in both directions over time, the dominant theoretical relationship is chosen.

Table 2 Demographics of the study population

Variable	Asthma severity algorithm			Acute asthma	
	No asthma	Diagnosis only or intermittent bronchodilator	Persistent mild*	Persistent moderate or severe	Inpatient hospital admission†
N	75 156	2839	6247	1664	3487
Sex=male (%)	37 906 (50)	1624 (57)	3767 (60)	1026 (62)	2284 (66)
Gestation at birth‡					
≤32	990 (1)	73 (3)	180 (3)	56 (3)	152 (4)
33–36	3974 (5)	173 (6)	390 (6)	131 (8)	245 (7)
37+ weeks	65 870 (88)	2429 (86)	5339 (86)	1389 (84)	2913 (84)
Small for gestational birth (<10th centile)‡=yes (%)	6474 (9)	272 (10)	578 (9)	141 (9)	337 (10)
Parity ≥1	43 284 (58)	1564 (55)	3572 (57)	947 (57)	2079 (60)
Congenital anomaly§=Yes (%)	3516 (5)	187 (7)	373 (6)	115 (7)	273 (8)
Maternal age at childbirth					
<18 (%)	1956 (3)	119 (4)	163 (3)	37 (2)	125 (4)
18–24 (%)	18 713 (25)	878 (31)	1857 (30)	502 (30)	1126 (32)
25–29 years (%)	21 072 (28)	802 (28)	1776 (28)	470 (28)	947 (27)
30–34 (%)	21 750 (29)	696 (25)	1622 (26)	434 (26)	868 (25)
35+ (%)	11 627 (16)	343 (12)	826 (13)	219 (13)	420 (12)
Breast feeding¶					
No (%)	28 242 (38)	1138 (40)	2602 (42)	716 (43)	1540 (44)
Yes (%)	31 996 (43)	1054 (37)	2282 (37)	661 (40)	1318 (38)
NA (%)	14 918 (20)	647 (23)	1363 (22)	287 (17)	629 (18)
Maternal smoking in first trimester					
No (%)	18 493 (25)	622 (22)	1351 (22)	382 (23)	729 (21)
Yes (%)	5448 (7)	243 (9)	491 (8)	130 (8)	308 (9)
NA (%)	51 215 (68)	1974 (70)	4405 (70)	1152 (69)	2450 (70)
Townsend deprivation quintile at birth					
1—least (%)	13 723 (18)	424 (15)	920 (15)	218 (13)	460 (13)
2 (%)	14 745 (20)	466 (16)	1102 (18)	307 (18)	593 (17)
3 (%)	15 171 (20)	561 (20)	1244 (20)	340 (20)	676 (19)
4 (%)	15 414 (21)	609 (22)	1414 (23)	390 (23)	824 (24)
5—most (%)	15 884 (21)	768 (27)	1547 (25)	403 (24)	921 (26)
Free school meals eligible**=yes (%)	12 299 (16)	643 (23)	1270 (20)	338 (20)	796 (23)
School absence percentage††					
<5 (%)	19 867 (48)	608 (41)	1254 (39)	297 (31)	624 (33)
5–9 (%)	12 776 (31)	476 (32)	1162 (36)	332 (35)	679 (36)
10–14 (%)	4473 (11)	196 (13)	462 (14)	174 (18)	300 (16)
15–19 (%)	1533 (4)	75 (5)	141 (4)	70 (7)	117 (6)
20+ (%)	922 (2)	60 (4)	111 (3)	44 (5)	92 (5)
NA (%)	1479 (4)	73 (5)	117 (4)	38 (4)	83 (4)

*Inhaled corticosteroid or alternative.

†Excludes first admission if before first GP visit.

‡6% missing data evenly found across asthma groups.

§Major or minor.

¶At birth or 6–8 weeks.

**In Key Stage 1 (KS1), assessment year as a proxy for level of deprivation beyond birth.

††In school year when KS1 was taken where assessment usually starts in the final 2½ months, subsample due to availability of school absence data, births between September 2000 and August 2004, N=46 470.

Following adjustment for social deprivation, birth and school characteristics, only asthma inpatient hospital admission remained associated with increased risk for not attaining the expected level at KS1 (aOR 1.14 95% CI (1.02 to 1.27)). Presentations to primary care for respiratory tract infections (RTIs) were also independently associated with increased risk for not attaining the expected level at KS1, aOR 1.15 95% CI (1.06 to 1.24) for three or more presentations for LRTI, and aOR 1.08 95% CI (1.01 to 1.16) for seven or more URTI GP contacts (table 5).

There was no evidence for interactions between the asthma severity algorithm GP categories or asthma inpatient hospital admissions, or between the asthma severity variables and other respiratory illness including LRTI and URTI, sex of the child or deprivation at the 5% level of significance. The increased risk in unadjusted ORs in the asthma severity algorithm categories, fell to a third of their size when inpatient hospital admission was added to the model, and then became non-significant at the 5% level when a measure of deprivation, gender or LRTI was added to the model. Model goodness of fit tests found interactions between confounders were only adjustments to main effects (in opposing

directions if significant at $p<0.05$ with no monotonic pattern) and therefore were not included in the final model interpretation (data not shown).

Very similar results were found for the wheeze severity algorithm and non-attainment of the expected level at KS1 (table 5).

Further analyses using asthma variables divided into age groups found no association for current chronic asthma severity, but higher odds for not attaining the expected level at KS1 for three or more inpatient hospital admissions aOR 1.4 95% CI (1.0 to 2.0) in children age 2–<5 years, with similar results for 0–<2 years and 5–<7 years. For wheeze or asthma, only three or more inpatient hospital admissions from age 2 years onwards had an increased association for not attaining the expected level at KS1 (online supplemental table S7).

A subsample analysis of births from 1 September 2000 to 31 August 2004 (where school absence data were available) showed after adjustment for school absence asthma inpatient hospital admissions were no longer associated with risk for not attaining the expected level at KS1 (aOR 1.05 (95% CI 0.90 to 1.24), but LRTI remained an independent predictor (aOR 1.13 (95% CI 1.02

Table 3 Asthma severity algorithms and acute asthma

Variable	Asthma severity algorithm* n (%)	Acute asthma (hospital inpatient admission)† n (%)	Wheeze severity algorithm‡ n (%)	Acute asthma or wheeze (hospital inpatient admission)§ n (%)
N	85 906	3487 (4.1)	85 906	4668 (5.4)
None	75 156 (87.5)	0 (0)	67 508 (78.6)	0 (0)
Diagnosis only	532 (0.6)	169 (32)	2237 (2.6)	683 (30.5)
Intermittent bronchodilator	2307 (2.7)	474 (21)	6465 (7.5)	938 (14.5)
Persistent mild	6247 (7.3)	1978 (32)	7964 (9.3)	2164 (27.2)
Persistent moderate	1365 (1.6)	661 (48)	1407 (1.6)	673 (47.8)
Persistent severe	299 (0.3)	205 (69)	325 (0.4)	210 (64.6)

Developed with an asthma diagnosis.

†Developed with either a wheeze or asthma diagnosis.

‡Excludes first admission if before first general practice visit.

to 1.26)) (online supplemental table S8). Similar results were found for not attaining the expected level at KS1 for acute asthma or wheeze when absence from school was added to the model.

Models with only one child per mother in the cohort showed no substantial difference to our main results, indicating that there was no problematic underestimation of variances arising through correlation between mothers.

DISCUSSION

Our results show that children with an inpatient hospital admission for asthma was associated with an increased risk for not attaining the expected level at KS1 at age 6–7 years after controlling for current asthma severity, deprivation, birth characteristics, other respiratory illness and school characteristics. Very similar results were obtained using a broader definition of asthma which included wheeze. Presentations to primary care for respiratory infections, particularly LRTI, were independently associated with not attaining the expected level at KS1, even after adjustment for school absence. We found no interaction between asthma and LRTI, or asthma and URTI for educational attainment outcome. We found school absence in the year a child takes KS1 assessment may be a potential mediator in the

association between asthma hospital admissions and not attaining the expected level at KS1.

This is the first study that explores the association of asthma and common respiratory ailments on educational attainment in childhood. The findings suggest that inpatient hospital admissions for asthma and recurring respiratory illness from birth to KS1 can have long-term effects on a child through their educational attainment.

The use of a second algorithm that included wheeze allowed us to investigate potentially under-reported asthma, particularly relevant to children under 5 years. It highlights that children treated for only wheeze through hospital admission were associated with increased risk for not attaining the expected level at KS1.

In previous research, GP data and parental surveys recording GP diagnosis of asthma^{1–3} in the UK, USA and Australia show similar results for this age group, reassuring us of the validity and classification of asthma in our study. For children with wheeze or asthma diagnosis, our UK prevalence matches a global survey,⁵ but is slightly lower than other UK surveys,^{4,30} most likely due to differences in cohort demographics.

In previous cohorts or surveys in population representative studies adjusted for confounding from deprivation (or proxy such as

Table 4 Respiratory illness between birth and before Key Stage 1 assessment by asthma severity

	Asthma severity algorithm						Acute asthma
	No asthma	Diagnosis only	Intermittent bronchodilator	Persistent mild*	Persistent moderate	Persistent severe	Inpatient hospital admission†
N	75 156	532	2307	6247	1365	299	3487
LRTI GP contacts§							
0 (%)	52 170 (69)	346 (65)	1071 (46)	2515 (40)	445 (33)	71 (24)	1196 (34)
1 (%)	13 361 (18)	94 (18)	520 (23)	1443 (23)	291 (21)	50 (17)	765 (22)
2 (%)	5336 (7)	48 (9)	319 (14)	863 (14)	207 (15)	30 (10)	511 (15)
3+ (%)	4289 (6)	44 (8)	397 (17)	1426 (23)	422 (31)	148 (50)	1015 (29)
URTI GP contacts							
0 (%)	20 266 (27)	204 (38)	427 (19)	1022 (16)	169 (12)	25 (8)	598 (17)
1–4 (%)	39 817 (53)	243 (46)	1195 (52)	3167 (51)	614 (45)	126 (42)	1663 (48)
5–6 (%)	7190 (10)	39 (7)	301 (13)	855 (14)	204 (15)	52 (17)	472 (14)
7+ (%)	7683 (10)	46 (9)	384 (17)	1203 (19)	378 (28)	96 (32)	754 (22)
GP contacts							
Influenza and pneumonia 1+ (%)	2067 (3)	20 (4)	82 (4)	304 (5)	113 (8)	16 (5)	242 (7)
Bronchiolitis 1+ (%)	3063 (4)	30 (6)	221 (10)	662 (11)	189 (14)	54 (18)	538 (15)
Chronic lower respiratory disease 1+ (%)	465 (1)	6 (1)	28 (1)	96 (2)	32 (2)	6 (2)	89 (3)
Unspecified respiratory illness 1+ (%)	392 (1)	<5 (0)	24 (1)	39 (1)	15(1)	<5 (1–2)	20 (1)
Chronic upper respiratory disease GP contacts							
0 (%)	69 704 (93)	490 (92)	2006 (87)	5250 (84)	1050 (77)	244 (82)	2907 (83)
1 (%)	4192 (6)	31 (6)	207 (9)	699 (11)	203 (15)	40 (13)	418 (12)
2+ (%)	1260 (2)	11 (2)	94 (4)	298 (5)	112 (8)	15 (5)	162 (5)
Croup GP contacts¶							
0 (%)	69 722 (93)	500 (94)	2077 (90)	5543 (89)	1146 (84)	239 (80)	3091 (89)
1+ (%)	5434 (7)	32 (6)	230 (10)	704 (11)	219 (16)	60 (20)	396 (11)

*Inhaled corticosteroid or alternative.

†Excludes first admission if before first GP visit.

§Includes bronchiolitis if coded with bronchitis.

¶Original categories 0, 1, 2+ changed due to small numbers concerning anonymity rules.

GP, general practice; URTI, upper respiratory tract infection.

Table 5 Multilevel multivariable models of asthma severity algorithm, respiratory illness and not attaining the expected level at Key Stage 1 (at 6–7 years)

	Not attained/Total (%)	Unadjusted OR (95% CI)	Asthma severity algorithm Multivariable* OR (95% CI)	Wheeze severity algorithm Multivariable* OR (95% CI)
N	14 935/85 906 (17)			
Asthma severity algorithm				
None (ref)	12 733/75 156 (17)	Ref	Ref	NA
Diagnosis only	134/532 (25)	1.58 (1.29 to 1.95)	1.21 (0.97 to 1.52)	NA
Intermittent bronchodilator	444/2307 (19)	1.11 (1.00 to 1.24)	0.90 (0.79 to 1.01)	NA
Persistent mild	1260/6247 (20)	1.21 (1.13 to 1.30)	0.97 (0.89 to 1.05)	NA
Persistent moderate	298/1365 (22)	1.36 (1.18 to 1.55)	1.06 (0.91 to 1.24)	NA
Persistent severe	66/299 (22)	1.45 (1.09 to 1.93)	1.02 (0.75 to 1.40)	NA
Hospital inpatient admission (acute asthma)†=yes (%)	837/3487 (24)	1.48 (1.36 to 1.61)	1.14 (1.02 to 1.27)	NA
Wheeze severity algorithm				
None (ref)	11 252/67 508 (17)	Ref	NA	Ref
Diagnosis only	451/2237 (20)	1.24 (1.11 to 1.39)	NA	1.05 (0.94 to 1.19)
Intermittent bronchodilator	1271/6465 (20)	1.20 (1.12 to 1.28)	NA	1.01 (0.94 to 1.08)
Persistent mild	1582/7964 (20)	1.22 (1.14 to 1.29)	NA	0.97 (0.90 to 1.04)
Persistent moderate	306/1407 (22)	1.37 (1.20 to 1.57)	NA	1.06 (0.91 to 1.23)
Persistent severe	73/325 (23)	1.53 (1.16 to 2.00)	NA	1.08 (0.80 to 1.45)
Hospital inpatient admission (acute asthma or wheeze)†=yes (%)	1112/4668 (24)	1.48 (1.37 to 1.59)	NA	1.14 (1.04 to 1.25)
LRTI‡ GP contacts§ (ref=none)				
1	2729/15 759 (17)	1.05 (1.00 to 1.10)	1.01 (0.96 to 1.07)	1.01 (0.96 to 1.06)
2	1260/6803 (18)	1.14 (1.07 to 1.22)	1.05 (0.97 to 1.13)	1.04 (0.97 to 1.12)
3+	1421/6726 (21)	1.33 (1.25 to 1.43)	1.15 (1.06 to 1.24)	1.14 (1.06 to 1.23)
URTI¶ GP contacts (ref=none)				
1–4	7727/45 162 (17)	0.98 (0.93 to 1.02)	1.00 (0.95 to 1.05)	1.00 (0.95 to 1.05)
5–6	1483/8641 (17)	1.00 (0.93 to 1.07)	1.01 (0.94 to 1.09)	1.01 (0.94 to 1.09)
7+	1842/9790 (19)	1.10 (1.03 to 1.17)	1.08 (1.01 to 1.16)	1.08 (1.00 to 1.16)
GP contacts				
Influenza and pneumonia 1+ (ref=None)	436/2602 (17)	0.96 (0.86 to 1.07)	NA	NA
Bronchiolitis 1+ (ref=none)	884/4219 (21)	1.26 (1.16 to 1.36)	1.01 (0.93 to 1.10)	1.00 (0.92 to 1.09)
Chronic lower respiratory disease 1+ (ref=none)	156/633 (25)	1.39 (1.15 to 1.69)	1.18 (0.96 to 1.45)	1.18 (0.96 to 1.45)
Unspecified respiratory illness 1+ (ref=none)	69/475 (15)	0.75 (0.57 to 0.98)	NA	NA
Chronic upper respiratory disease GP contacts (ref=none)				
1	914/5372 (17)	0.98 (0.91 to 1.06)	NA	NA
2+	308/1790 (17)	1.02 (0.90 to 1.16)	NA	NA
Croup GP contacts (ref=none)				
1	884/5247 (17)	0.98 (0.91 to 1.06)	NA	NA
2+	264/1432 (18)	1.14 (0.99 to 1.31)	NA	NA
Townsend deprivation quintile				
1—least (ref)	1517/15 285 (10)	Ref	Ref	
2	2271/16 620 (14)	1.27 (1.18 to 1.37)	1.16 (1.07 to 1.25)	1.16 (1.07 to 1.25)
3	2944/17 316 (17)	1.53 (1.42 to 1.65)	1.28 (1.18 to 1.38)	1.28 (1.18 to 1.38)
4	3494/17 827 (20)	1.84 (1.71 to 1.98)	1.42 (1.32 to 1.54)	1.42 (1.32 to 1.54)
5—most	4668/18 602 (25)	2.32 (2.16 to 2.49)	1.54 (1.42 to 1.67)	1.54 (1.42 to 1.67)

*Adjusted for all variables in the table significant at the 5% level in unadjusted analyses, sex, gestation at birth, small for gestational age (<10th centile), parity, major or minor congenital anomalies, maternal age (25–29 years, <18, 18–24, 30–34, 35+), breast feeding at birth or 6–8 weeks, maternal smoking in first trimester, free school meals in school year take KS1 assessment (to approximate deprivation beyond birth), academic season of birth (autumn, spring, summer), school moves from start school to KS1 (1+), urban or rural (inc. town) dwelling at birth, year take Key Stage 1 (ref 2010).

†Excludes first admission if before first GP visit.

‡Lower respiratory tract infection.

§Includes bronchiolitis if coded with bronchitis.

¶Upper respiratory tract infection.

GP, general practice; LRTI, lower respiratory tract infection.

maternal education), a detrimental association of current asthma (defined as with a prescription) at age 6 years was found for reading (aOR 2.20 95% CI (1.08 to 4.51))¹⁷ (measured as ≥6 months behind), but with no difference in mathematics in New Zealand. In the USA, asthma defined as requiring attention or treatment in the last year and limiting a child's activity found children less likely to be school ready, but no difference in language skills compared with children without asthma.¹⁸

Another study found no significant difference ($p>0.05$) for children age 5–7 years in parental reporting for repeating a school year.¹⁴ None of these studies separated chronic asthma severity and acute asthma or adjusted for the full range of respiratory illness, school or birth characteristics (the latter study only adjusting for birth weight).

Other cohorts that adjusted for deprivation used wider age bands (children 5–16 years), found no association^{12,13} with asthma, possibly due to adjustment for SEN provision,¹³ or concluded that lower marks

were explained by higher days absent.¹⁶ A Canadian study found children with severe asthma (defined as using asthma medication) was associated with poorer mathematics scores but not in reading.¹⁹ None of these studies adjusted for birth characteristics or other respiratory illnesses and our smaller adjusted risks demonstrate the importance of controlling for confounding. At key developmental ages, younger children may have greater risk of hospital admission for asthma or wheeze as they experience potentially more associated RTIs at younger ages,³⁰ and may be less able to communicate symptoms or manage their condition.

Studies measuring absence from school as an outcome³¹ or in addition to educational attainment^{12,16,17,19} mostly reported 2 more days absence in a year compared with children without asthma, and higher absence for younger children.³² When more severe asthma was measured using reliever prescriptions or emergency department visits, children had 7 or more days absence from school in a year,^{19,31}

and agree with the higher proportions of absence we found across our categories for children with asthma compared with those without (table 2).

Consistent with other studies,^{13,33} we found higher prevalence of asthma in children living in more deprived areas, possibly due to poorer housing conditions,³³ environmental factors or less healthy diets⁵ that could also lead to more RTIs.

Strengths

Clinical diagnosis in our algorithms mean records of medications that sometimes have other uses, a bronchodilator medication trial over 6 weeks or reversibility test at the clinician appointment are most likely excluded. General practitioners have indicated that symptoms used to classify severity of asthma or wheeze may not be fully recorded during GP consultations but inform prescribing, therefore using prescriptions should minimise any selection or ascertainment bias.

The use of routine data from clinical practitioners on diagnoses and prescriptions rather than parental reports removes the potential impact of recall bias.

Limitations

Hospital admission policies may differ across Wales, but testing models with local education authorities (the same geographical areas as health boards before 2009) shows little correlation and minimal selection bias. Some families contact their GP more often than others; but any additional visits to the GP would bias risk for not attaining the expected level at KS1 towards the null (more visits would be required to show a significant association). Children in more deprived areas may be less compliant to asthma management plans; we found no effect modification between chronic asthma severity or acute asthma and our measures of deprivation for educational attainment, residual confounding may remain, but would only highlight that barriers to health still exist.

This study does not include accident and emergency admissions data, and may underestimate the number of attendances for acute asthma exacerbations; an audit showed 86% of exacerbations were treated in GP in 1991.³⁴ Our study only investigated period prevalence; a recent paper investigating worsening asthma in the previous year found an association with poorer educational attainment.³⁵

This study uses a large population-based representative cohort with asthma or wheeze severity algorithms akin to asthma management guidelines found in the USA and UK. Only 5% of children move out of Wales each year, and GP data included were found to represent the Welsh population so results should be generalisable in the UK and other countries with similar sociodemographic and health systems.

Implications for research and practice

Clinicians and educators need to be aware that children who have inpatient hospital admissions for asthma or wheeze, or repeated LRTI GP visits, may need additional educational support for their educational outcomes. For children with asthma, the association between LRTI and not attaining the expected level at KS1 was not above that expected for children without asthma, but more children with asthma had multiple GP visits for LRTI (indicating accumulating risk).

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Contributors SP, DF and AE conceived the idea for this project. AE, SP, DF designed the study and developed the analysis plan. CVEP gave advice on clinical diagnosis and study design. JD and AB extracted the data and prepared

the datasets for analysis. AE developed the datasets for statistical analysis and analysed the data. AE carried out the literature searches and wrote the first draft of the paper. All authors were involved in interpreting the findings, revising drafts and agreeing with the final version.

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Data availability statement Data are available upon reasonable request. Data are available from the SAIL Databank at HDRUK Swansea University <https://saildatabank.com/> or contact ku.ca.aesnews@knabataDLIAS. For further information on access including training required see website: <https://saildatabank.com/application-process/following-approval/#remote-access>. For new projects see <https://saildatabank.com/application-process/two-stage-process/>. We confirm that interested researchers can contact the SAIL Databank directly to request access to the data used in this study, and all information necessary to do so is found at these websites. We confirm that the authors did not have any special access privileges that others would not have.

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REFERENCES

- Punekar YS, Sheikh A. Establishing the incidence and prevalence of clinically diagnosed allergic conditions in children and adolescents using routinely collected data from general practices. *Clin Exp Allergy* 2009;39:1209–16.
- Henderson J, Charles J, Pan Y, et al. Management of childhood asthma in general practice. *Aust Fam Physician* 2015;44:349–51.
- Zahrn HS, Bailey CM, Damon SA, et al. Vital Signs: Asthma in Children - United States, 2001–2016. *MMWR Morb Mortal Wkly Rep* 2018;67:149–55.
- Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–80.
- Lai CKW, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International study of asthma and allergies in childhood (ISAAC). *Thorax* 2009;64:476–83.
- Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;14:113.
- National Heart, Lung, and Blood Institute. National asthma education and prevention program: expert panel report 3: guidelines for the diagnosis and management of asthma, full report. US department of health and human services, 2007.
- British Thoracic Society and Scottish Intercollegiate Guidelines Network. Sign British guideline on the management of asthma: a national clinical guideline. Healthcare Improvement Scotland, 2019.
- Helms PJ, Henderson J. Respiratory disorders. In: McIntosh N, Helms PJ, Smyth RL, eds. *Textbook of pediatrics*. 6th edn. London: Churchill Livingstone, 2003: 774–5.
- Heikkinen T, Järvinen A. The common cold. *The Lancet* 2003;361:51–9.
- Fraenkel DJ, Bardin PG, Sanderson G, et al. Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. *Am J Respir Crit Care Med* 1995;151:879–86.
- Mooney S, Sterling DA, Figgs LW, et al. The relationship between school absence, academic performance, and asthma status. *J Sch Health* 2008;78:140–8.
- Sturdy P, Bremner S, Harper G, et al. Impact of asthma on educational attainment in a socioeconomically deprived population: a study linking health, education and social care datasets. *PLoS One* 2012;7:e43977.
- Byrd RS, Weitzman ML. Predictors of early grade retention among children in the United States. *Pediatrics* 1994;93:481–7.
- Fowler MG, Davenport MG, Garg R. School functioning of US children with asthma. *Pediatrics* 1992;90:939–44.
- Crump C, Rivera D, London R, et al. Chronic health conditions and school performance among children and youth. *Ann Epidemiol* 2013;23:179–84.
- Liberty KA, Patterson P, Reid J, et al. Beginning school with asthma independently predicts low achievement in a prospective cohort of children. *Chest* 2010;138:1349–55.
- Haltermann JS, Montes G, Aligne CA, et al. School readiness among urban children with asthma. *Ambul Pediatr* 2001;1:201–5.
- Kohen DE. Asthma and school functioning. *statistics Canada health reports*. 21, 2010.
- Ford DV, Jones KH, Verplanck J-P, et al. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res* 2009;9:1572.
- Lyons RA, Jones KH, John G, et al. The SAIL databank: linking multiple health and social care datasets. *BMC Med Inform Decis Mak* 2009;9:3.
- Lyons RA, Hutchings H, Rodgers SE, et al. Development and use of a privacyprotecting total population record linkage system to support observational, interventional, and policy relevant research. *The Lancet* 2012;380:56.
- National Foundation for Education Research (NFER). Statutory assessment in compulsory education in Wales: summary table. Available: <http://www.nfer.ac.uk/nfer/index.cfm?AE4CD07-C29E-AD4D-0B50-575F25B37AA9> [Accessed 2 Jul 2013].
- Asthma in Swansea: Report of a study to examine the prevalence of asthma throughout the City and County of Swansea using the Secure Anonymised Information Linkage (SAIL) system. National Public Health Service for Wales, 2009. Available: https://www.google.co.uk/url?sa=t&src=8&source=web&cd=3&ved=0ahUKEwjYt-saa6-7bAhUEJ8AKHRe1DroQFggwMAI7bAhUEJ8AKHRe1DroQFggwMAI8url=http%3A%2F%2Fwww.2.nphs.wales.nhs.uk%3A8080%2FHATDocs.nsf%2F%24all%2F2020EC097E17B4E08802576EA004918472F020EC097E17B4E08802576EA004918472F24file%2FSAI1AsthmaSwansea_Findings_V2b.doc%3FOpenElement&usq=A0v-Vaw3nCbogOpdYHC8OSJFQFR2IAOvVaw3nCbogOpdYHC8OSJFQFR2I [Accessed 1 Jul 2018].
- Paediatric Formulary Committee. British National formulary for children (BNFC) 2016–2017. London: BMJ group and pharmaceutical press, 2016. <https://bnf.nice.org.uk/>
- Textor J, van der Zander B, Gilthorpe MS, et al. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2016;45:1887–94.
- Evans A, Dunstan F, Fone DL, et al. The role of health and social factors in education outcome: a record-linked electronic birth cohort analysis. *PLoS One* 2019;14:e0220771.
- Jiang Z, VanderWeele TJ. When is the difference method conservative for assessing mediation? *Am J Epidemiol* 2015;182:105–8.
- Royston P, White I. Multiple Imputation by Chained Equations (MICE): Implementation in Stata. *J Stat Softw* 2011;45.
- Griffiths LJ, Lyons RA, Bandyopadhyay A, et al. Childhood asthma prevalence: cross-sectional record linkage study comparing parent-reported wheeze with general practitioner-recorded asthma diagnoses from primary care electronic health records in Wales. *BMJ Open Respir Res* 2018;5:e000260.
- Sullivan PW, Ghushchyani V, Navaratnam P, et al. The National burden of poorly controlled asthma, school absence and parental work loss among school-aged children in the United States. *Journal of Asthma* 2018;55:659–67.
- Taras H, Potts-Datema W. Childhood asthma and student performance at school. *Journal of school health* 2005;75:296–312.
- Hancox RJ, Milne BJ, Taylor DR, et al. Relationship between socioeconomic status and asthma: a longitudinal cohort study. *Thorax* 2004;59:376–80.
- Neville RG, Clark RC, Hoskins G, et al. National asthma attack audit 1991–2. *BMJ* 1993;306:559–62.
- Pattamore PK, Liberty KA, Reid J. Changes in asthma severity in the first year of school and difficulty learning to read. *J Asthma* 2020;57:799–809.

Capacitar crianças e jovens asmáticos

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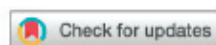
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RESUMO

A asma é a condição crónica mais comum da infância. Nesta revisão, discutimos uma visão geral das estratégias para capacitar as crianças e os jovens asmáticos. Os aspetos essenciais da capacitação vão no sentido de permitir uma tomada de decisão partilhada e da auto-gestão e de ajudar as crianças a minimizarem o impacto da asma na sua vida. As evidências de apoio a estas estratégias são escassas ou heterogêneas, sendo difícil identificar quais as intervenções com maior probabilidade de melhorar os resultados clínicos. Determinantes de saúde mais amplos, em contextos de recursos altos e baixos, podem ser desmotivantes para as crianças asmáticas. Novas abordagens tecnológicas poderiam ajudar a capacitar os jovens asmáticos ou com condições de saúde crónicas distintas.

INTRODUCTION

Various frameworks have attempted to describe what 'empowerment' means for people with chronic conditions.^{1,2} The key elements are to enable people to contribute to decisions about their health, self-manage as much as possible and tailor their condition around their life. In this paper, we provide an overview of strategies that empower children and young people (CYP) with asthma. Where possible, we use evidence from systematic reviews of randomised controlled trials (RCTs) in CYP with asthma. The process of development through childhood carries specific problems for different age groups. We generally refer to CYP as being people at school (ie, aged 6–16 years), although some discussions will be relevant to young adults. We do not address the process of how to run transition clinics or develop services that move CYP from paediatric to adult services, as a detailed description of this important problem is outside the remit of this paper.

Most CYP can achieve asthma control with inhaled corticosteroids (ICS), aeroirritant avoidance and healthy lifestyle. Guidelines to date recommend that CYP use metered dose inhaler, via spacer, to deliver ICS and add long-acting beta-agonist (LABA) or oral antileukotriene agents such as montelukast if needed.³ The vast majority of CYP referred to tertiary services get better with simple changes, rather than escalation of medication for severe treatment-resistant asthma.^{4,5} Newer approaches are to use combination inhalers containing ICS and long-acting and fast-acting bronchodilator as both maintenance and reliever therapy,⁶ or to use ultra-long-acting ICS (fluticasone furoate) and LABA (vilanterol) in a once-daily preparation.⁷ Despite these, some CYP will step up to injectable biologic therapies, which can be selected in a targeted and personalised way.^{8,9}

In box 1, we present the views of a young person, who recently transitioned to adult services. We asked "can you tell us what you want from your life, how asthma gets in the way, and things

What is already known on this topic?

- ▶ Chronic illness affects children's health, and health-related quality of life.
- ▶ Empowering people with chronic illness can be beneficial.
- ▶ Empowering people is a focus of the National Health Service long-term plan.

What is already known?

- ▶ We propose a framework for what empowerment entails: shared decisions, self-management and living a normal life.
- ▶ We discuss how the evidence base behind strategies for how to empower children with asthma is currently lacking.
- ▶ We share the views of a young person, describing how asthma affected her childhood.

which happen in clinic which make you feel in control, or not in control".

This account reflects difficulties that CYP with asthma have, and concerns of their parents. Our goals as healthcare professionals are to keep CYP with asthma safe and reduce the risk of complications. We also need to focus on enabling CYP to make the most of their opportunities and live without fear. Adolescence is a time to develop independence and, as highlighted in this account, asthma can impede this.

Making shared decisions about healthcare

Paternalistic models of healthcare, in which clinicians make decisions on behalf of patients, are now considered old-fashioned. CYP, and their parents, should be involved in making decisions about their health. The General Medical Council requires that doctors work in partnership with patients, by listening to their preferences, giving information in a meaningful way and respecting their right to reach decisions.¹⁰

Tools to enable shared decisions in childhood asthma have been evaluated in two RCTs, both in primary care. One study failed to recruit sufficient participants.¹¹ In the other study, 60 families were randomised to use a shared decision-making portal or usual care.¹² For the primary outcome (acceptability of asthma care at 6 months), there was no difference between groups, but families using the portal reported improvements in rates of asthma attacks and school absenteeism. In prospective cohort studies, also in primary care, use of a toolkit to aid shared decisions was associated with improved asthma control and reduced asthma attacks.^{13,14}

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What is already known on this topic?

As a child, asthma was always a big problem in mine and my families lives. It did prevent me from a few opportunities in my life such as school trips, and a few days out with friends. I wasn't allowed to go anywhere on my own, because of the risk of me having an attack and nobody being around to help me. I also couldn't take part in sports such as football which I have always loved. I always felt like I was the decision maker when it came to my treatment and my health when under Alder Hey. I felt that the respiratory team were always open and honest about the treatment and support they could provide me with. I am grateful for the support they provided me with, especially with school. The respiratory team visited my school to ensure that there were trained staff to deal with the condition. This gave both myself and my parents peace of mind when I was attending school unwell. I was very proud to have passed all of my exams and attend my high school prom, something that my family and I never thought I would be able to do.

Throughout my childhood I felt as though I was very reliant on other people to get me to school, and to places where I was meeting friends, as my parents didn't like me getting the bus on my own. This made me feel like I had no freedom, I had to ask to be taken somewhere all the time. My asthma was definitely the main focus of my childhood. It was also the main focus of my parents and my grandparents for the most part. If we were to be doing something they always had to think about my asthma and could it cause an attack. Things like going on a day out with my cousins and my grandparents, there would always be things my cousins could do that I couldn't take part in, in case I had an attack. If I was to be staying over at anybody's house, my mum would have to have a chat with them first to make sure they knew what to do if I did have an attack and how to spot my signs.

I believe that most of my asthmatic episodes were due to the air pollution in and around Runcorn. I moved to Cornwall in 2018, because the air is so much cleaner and as a result of this I haven't had an admission to hospital since. I am still taking large amounts of drugs to control the asthma but feel that I am now more in control of the condition rather than it controlling me. I am now able to play football for a local Sunday league team and I went on an over seas trip to Canada with my college in February 2019.

The key to making shared decisions effectively is to acknowledge viewpoints of the clinician and the person with the illness.¹⁵

In paternalistic models of care, the clinician decides on a treatment choice after delivering medical information to a patient; in a shared approach the clinician and person with an illness make the choice together after a two-way exchange of both medical and personal information.¹⁶ This should involve delivery of understandable, balanced, evidence-based information, support for the person making decisions about their healthcare, and a system for recording, communicating and implementing preferences.¹⁷ Figure 1 outlines an approach to making shared decisions, in which information from healthcare professionals and people with chronic illnesses can be used to reach a mutually acceptable plan.

Healthcare professionals, parents and CYP may be uncomfortable with the communication style required to make sha-

red decisions—indeed, some families may prefer the clinician to make all the decisions. Visual aids, role-playing and actively involving CYP in discussions can be useful.¹⁸ It is important to acknowledge that people may have sought health information from the internet and social media.¹⁹ This should be seen as a positive aspect of a patient starting taking control of their health, and healthcare professionals should not feel undermined, nor appear dismissive. It is important to discuss the validity of information on websites and social media, as the quality of such forums is variable.²⁰

Guidelines and flow charts can enable evidence-based practice, by providing a framework for treatment choices. In most situations, however, decision-making is nuanced and complex, as is interpretation of clinical research. This is reflected in differences between guidelines for CYP with asthma, which vary in diagnostic and therapeutic recommendations.²¹ Given that CYP with asthma respond to treatment in different ways,^{22 23} they should be offered personalised therapeutic options whenever possible.

Being able to self-manage

The aim of asthma management in CYP is to prevent symptoms and asthma attacks, so they can do things they would like. This should be done in a way that asthma becomes an additional consideration within their daily lives rather than the central focus of how the family functions. Supported self-management, which empowers people with asthma, reduces emergency healthcare utilisation, and improves health-related quality of life (HRQoL).²⁴

Using medication properly is a fundamental aspect of self-management. A systematic review including six large cohort studies found that better adherence to medication reduced the risk of asthma attacks requiring unscheduled visits to the emergency department (ED) or hospitalisation.²⁵ Reviews of observational studies report that inhaler technique is suboptimal, in patients^{26 27} and healthcare professionals.²⁸

A Cochrane review identified 39 trials, of which 18 were conducted in CYP, studying the effects of different types of technique for improving adherence to ICS.²⁹ These included educational approaches (individual and group sessions, motivational interviewing, family-based and team-work interventions, nurse led psychoeducation, telephone interventions and interactive voice recognition systems), electronic tracker/reminder systems, simplified drug regimes and directly observed therapy in schools. These approaches improve adherence (educational approaches and electronic inhaler tracker devices by around 20%, simplified drug regimes by 4%), but did not improve risk of asthma attacks, overall control or HRQoL.

Another important part of enabling self-care is to give families, in a written asthma action plan (AAP), a summary of treatment for when a child is well, and less well, and what to do during an asthma attack. Although AAPs should enable effective selfmanagement, hence their inclusion in guidelines,³⁰ the evidence around them is inconsistent. Systematic reviews and RCTs consistently show that AAPs do not affect health outcomes,^{31 32} but an overview of evidence around supported self-management concluded that AAPs should be a core component of the management of asthma.²⁴ Research is needed to identify how to develop the right action AAP for individual CYP. A meta-ethnography of qualitative research found several studies examining views around AAPs from parents and carers of children with asthma, but few from CYP themselves.³³ Another study found that readability of AAPs was variable,³⁴ and an RCT by the same group found that a simpler plan developed for people with low literacy levels was more effective.³⁵ A systematic review identified four RCTs comparing paper and smartphone AAPs.³⁶ One of these, a small pilot study with 34 participants, included only adolescents.³⁷ Although there was no difference in clinical outcomes, adolescents universally pre-

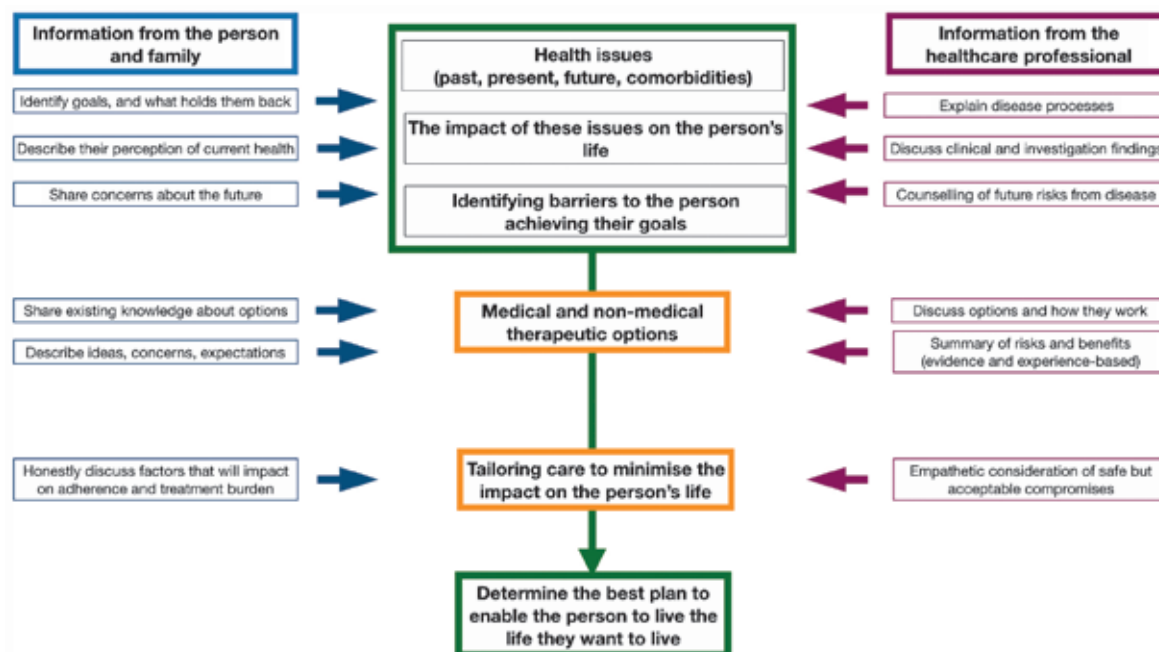


Figure 1 An approach to making shared healthcare decisions with young people.

ferred using smartphone-based action plans. To be useful, AAPs must be given alongside robust education, and tailored to individual CYP. There are uncertainties around what to include in an AAP, such as whether or not to increase the dose of ICS at times of worsening control.

There is interest in whether school-based educational interventions for CYP with asthma might improve self-management. A Cochrane mixed-methods review included 55 studies, of which 33 were RCTs.³⁸ The review found that school-based interventions for promoting self-management in CYP with asthma were successful in reducing unscheduled ED attendance or hospitalisation. The authors highlight the need for ongoing work but suggested that developing school-based interventions using a theoretical framework, engaging parents in the process and conducting sessions outside of the children's free time may help successful implementation. Another promising clinic strategy, tested in small pilot projects, is peer-group shared medical appointments, in which a group of CYP would be seen together.^{39–41}

Helping children and young people tailor their asthma around their life

All CYP have the right to feel happy and secure, live their best life and strive for their ambitions. It is incumbent on health professionals to help CYP make the most of their childhood. This involves being flexible, empathetic, compassionate and responsive to the needs of individual CYP.

In an international survey of 943 CYP with asthma, 490 (52%) felt that asthma made them 'different', including feeling unhealthy, like they were missing out, sad and unable to do exercise.⁴² In a qualitative study, 10 CYP were interviewed about how asthma affects their daily life.⁴³ They described how they had developed coping strategies so they had 'learnt to live' with asthma, did not want asthma to be the focus of their daily life, wanted people to acknowledge that asthma might hold them back without being overly sympathetic and felt that asthma limited their ability to do exercise. This reflects the views of the young person in box 1. More research is needed to evaluate the impact of asthma on school attendance. Studies to date show high levels of absenteeism,⁴⁴ and that this may be associated with asthma control,^{45–46} parental asthma⁴⁷ and environmental factors such as pollution.⁴⁸

Our group developed and piloted a community-based exercise and education programme for CYP with asthma, in response to children telling us that they found asthma to be an isolating

condition because they were unable to play during break times at school, missed school trips and were often excluded from physical activity lessons or social activities with their friends. The Set goals, Commit, Optimise therapy, Reinforce and Enable model was developed initially as a way of helping CYP with asthma become fit and healthy. When we evaluated the service, we found that the key benefit described by CYP was the opportunity to make friends, which improved their self-esteem, and this seemed to be reflected in improved asthma control.^{41–49}

Socioeconomic determinants of health

Development of asthma,⁵⁰ and subsequent asthma control,⁵¹ are strongly linked to many prenatal and postnatal environmental determinants including antenatal maternal stress⁵² and smoking,⁵³ postnatal secondhand smoke exposure,⁵⁴ poor quality housing,⁵⁵ obesity,⁵⁶ food poverty^{57–58} and air pollution.^{59–61} The aim of empowering young people with asthma is to give them control over their health and their lives. Socioeconomic deprivation is disempowering because it limits the lifestyle choices that people are able to make. Families living in poverty may have reduced access to healthy foods and resources to enable physical exercise. When promoting healthy lifestyles, professionals should be sensitive to the barriers that limit peoples' choices when they live in poverty. At a wider level, national and regional policies should be developed with the well-being of CYP as a central theme. Asthma outcomes can be amenable to upstream policy changes, as was seen when exacerbation rates were reduced by public smoking bans,^{62,63} and community-based projects to educate families about good asthma care, including housing advice.⁶⁴

Barriers to empowering children in low-income and middle-income countries

Low-income and middle-income countries (LMICs) face an increasing burden of asthma,^{65–66} and empowering CYP in the face of this could represent an important step towards improving outcomes. However, LMICs face many challenges, some of which do not necessarily affect more high-income countries. One barrier is the availability, cost and accessibility of healthcare, compounded by suboptimal medical insurance coverage.

Furthermore, young people's understanding of asthma, adherence to medications and appropriate use of healthcare resources are impeded by low levels of education and literacy, and strong negative perceptions and stigma associated with the disease.⁶⁷ Another problem, around which little research has been conduc-

ted, is the nature of the doctor-patient relationship in paediatrics in LMICs. Culturally, it is likely that in many settings this is still somewhat patriarchal and this may impede the process of making shared decisions.

How innovation might empower children and young people with asthma

We have discussed problems with getting the fundamental aspects of asthma management right-both at clinic and at home. Current technological advances have the potential to improve the lives of CYP with chronic conditions such as asthma. Health services have been traditionally slow to develop and adopt new technology, but recent investment and development of innovation networks across the UK should improve this.⁶⁸ A recent systematic review and meta-analysis of studies evaluating electronic health interventions (including mobile technology and telemedicine) found small but statistically significant improvements in adherence in 15 studies (1 of social media, 1 of electronic health records, 6 of telehealth and 7 of mobile health interventions).⁶⁹ Further work should identify which technological approaches improve clinical outcomes. Current technologies in development include wearable technology,⁷⁰ telehealth⁷¹ and how big data might help identify population-level trends in asthma severity⁷² and individual risks to enable self-management.⁷³ Many innovations in medicine fall by the wayside because they are not addressing a tangible problem of relevance to patients, or because they use a solution which in itself is burdensome or prohibitively expensive. Innovations in asthma should be co-developed with children and families to ensure they are useful and relevant.

SUMMARY

Health professionals should endeavour to empower CYP with asthma. This involves enabling them to make shared decisions, be as independent as possible and minimise the impact asthma has on their lives. Current strategies have not always been developed using a robust theoretical framework, and there is need for evidence from well-designed, large, RCTs. Further research should focus on issues around school in children with asthma, as this may identify areas in which care could be improved, and strategies to enable children to lead a normal life as possible. Approaches to empowerment should also focus on socioeconomic determinants of health, low-resource settings and development of appropriate technologies.

Twitter Olivia Fulton @just_TUX

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REFERENCES

- Bravo P, Edwards A, Barr PJ, et al. Conceptualising patient empowerment: a mixed methods study. *BMC Health Serv Res* 2015;15:252.
- Werbruggen A, Swinnen E, Kerckhofs E, et al. How to empower patients? A systematic review and meta-analysis. *Transl Behav Med* 2018;8:660-74.
- British Thoracic Society SIGN. BTS. SIGN guideline for the management of asthma 2019.
- Sharpley J, Gupta A, Fleming L, et al. Long-Term effectiveness of a staged assessment for paediatric problematic severe asthma. *Eur Respir J* 2012;40:264-7.
- Brown L, Worrall V, Lilley A, et al. A new regional multidisciplinary clinic for children with difficult asthma. *European Respiratory Journal* 2019;54.
- Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting β -agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma. *JAMA* 2018;319:1485.
- Rodrigo GJ, Plaza V. Once-Daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2016;116:565-70.
- Sagliani S, Bush A, Carroll W, et al. Biologics for paediatric severe asthma: trick or treat? *Lancet Respir Med* 2019;7:294-6.
- Busse WW. Biological treatments for severe asthma: a major advance in asthma care. *Allergol Int* 2019;68:158-66.
- General Medical Council, 2013. Available: https://www.gmc-uk.org/-/media/documents/Good_medical_practice_English_1215.pdf_51527435.pdf [Accessed 15 Dec 2019].
- van Bragt S, van den Beemt L, Kievits R, et al. PELICAN: a cluster-randomized controlled trial in Dutch general practices to assess a self-management support intervention based on individual goals for children with asthma. *J Asthma* 2015;52:211-9.
- Fiks AG, Mayne SL, Karavite DJ, et al. Parent-reported outcomes of a shared decisionmaking portal in asthma: a practice-based RCT. *Pediatrics* 2015;135:e965-73.
- Tapp H, Shade L, Mahabaleshwar R, et al. Results from a pragmatic prospective cohort study: shared decision making improves outcomes for children with asthma. *J Asthma* 2017;54:392-402.

- Welch M, Ludden T, Mottus K, et al. Patient and provider perspectives on uptake of a shared decision making intervention for asthma in primary care practices. *J Asthma* 2019;56:562-72.
- Rivera-Spoljaric K, Halley M, Wilson SR. Shared clinician-patient decision-making about treatment of pediatric asthma: what do we know and how can we use it? *Curr Opin Allergy Clin Immunol* 2014;14:161-7.
- Charles C, Gafni A, Whelan T. Decision-Making in the physician-patient encounter: revisiting the shared treatment decision-making model. *Soc Sci Med* 1999;49:651-61.
- Coulter A, Collins A. King's Fund Centre (London E. Making shared decision-making a reality: no decision about me, without me). London: King's Fund, 2011. Available: <http://www.kingsfund.org.uk/document.rm?id=9190> [Accessed 15 Dec 2019].
- Butz AM, Walker JM, Pulsifer M, et al. Shared decision making in school age children with asthma. *Pediatr Nurs* 2007;33:111-6.
- Ramsey RR, Carmody JK, Holbein CE, et al. Examination of the uses, needs, and preferences for health technology use in adolescents with asthma. *J Asthma* 2019;56:964-72.
- Banasik NC, Meadows-Oliver M. Evaluating asthma websites using the brief discern instrument. *J Asthma Allergy* 2017;10:191-6.
- White J, Paton JY, Niven R, et al. Guidelines for the diagnosis and management of asthma: a look at the key differences between BTS/SIGN and NICE. *Thorax* 2018;73:293-7.
- Lemanske RF, Mauger DT, Sorkness CA, et al. Step-Up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975-85.
- Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138:1608-18.
- Pinnock H, Parke HL, Panagioti M, et al. Systematic meta-review of supported selfmanagement for asthma: a health-care perspective. *BMC Med* 2017;15:64.
- Engelkes M, Janssens HM, de Jongste JC, et al. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015;45:396-407.
- Sanchis J, Gich I, Pedersen S, et al. Systematic review of errors in inhaler use: has patient technique improved over time? *Chest* 2016;150:394-406.
- Gillette C, Rockich-Winston N, Kuhn JA, et al. Inhaler technique in children with asthma: a systematic review. *Acad Pediatr* 2016;16:605-15.
- Plaza V, Giner J, Rodrigo GJ, et al. Errors in the use of inhalers by health care professionals: a systematic review. *J Allergy Clin Immunol Pract* 2018;6:987-95.
- Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst Rev* 2017;4:CD012226.
- Global Initiative for Asthma. GINA 2019 main report June-2019, 2019. Available: <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf> [Accessed 28 Dec 2019].
- Zemek RL, Bhogal SK, Ducharme FM. Systematic review of randomized controlled trials examining written action plans in children: what is the plan? *Arch Pediatr Adolesc Med* 2008;162:157-63.
- Villa-Roel C, Voklander B, Ospina MB, et al. Effectiveness of written action plans for acute asthma: a systematic review. *J Asthma* 2018;55:188-95.
- Ring N, Jepson R, Hoskins G, et al. Understanding what helps or hinders asthma action plan use: a systematic review and synthesis of the qualitative literature. *Patient Educ Couns* 2011;85:131-43.
- Yin HS, Gupta RS, Tomopoulos S, et al. Readability, suitability, and characteristics of asthma action plans: examination of factors that may impair understanding. *Pediatrics* 2013;131:e116-26.
- Yin HS, Gupta RS, Mendelsohn AL, et al. Use of a low-literacy written action plan to improve parent understanding of pediatric asthma management: a randomized controlled study. *J Asthma* 2017;54:919-29.
- Murphy JA, Heisser JM, Montgomery M. Evidence-Based review of smartphone versus paper asthma action plans on asthma control. *J Pharm Tech* 2019;35:126-34.
- Perry TT, Marshall A, Berlinski A, et al. Smartphone-Based vs paper-based asthma action plans for adolescents. *Ann Allergy Asthma Immunol* 2017;118:298-303.
- Harris K, Keane D, Lasserson T, et al. School-Based asthma self-management interventions for children and adolescents with asthma. *Paediatr Respir Rev* 2019;31:40-2.
- Fallon M, Haynes L, Cadet T, et al. A group visit for high-risk pediatric asthma patients: a quality improvement initiative to improve asthma care. *Clin Pediatr* 2019;58:746-51.
- Wall-Haas CL, Kulbok P, Kirchgessner J, et al. Shared medical appointments: facilitating care for children with asthma and their caregivers. *J Pediatr Health Care* 2012;26:37-44.
- Hepworth C, Lilley A, Gait L, et al. A multidisciplinary community-based complex intervention on children with asthma. *Eur Respir J* 2019;54.
- Wildhaber J, Carroll WD, Brand PLP. Global impact of asthma on children and adolescents' daily lives: the room to breathe survey. *Pediatr Pulmonol* 2012;47:346-57.
- Jonsson M, Schuster M, Protudier JLP, et al. Experiences of Daily Life Among Adolescents With Asthma - A Struggle With Ambivalence. *J Pediatr Nurs* 2017;35:23-9.
- Stridsman C, Dahlberg E, Zandén K, et al. Asthma in adolescence affects daily life and school attendance - Two cross-sectional population-based studies 10 years apart. *Nurs Open* 2017;4:143-8.
- Bacharier LB, Covar RA, Haselkorn T, et al. Consistently very poorly controlled asthma is associated with greater activity and school impairment in children with severe or difficult-to-treat asthma. *J Allergy Clin Immunol Pract* 2017;7:314-6.
- Hsu J, Qin X, Beavers SF, et al. Asthma-Related school absenteeism, morbidity, and modifiable factors. *Am J Prev Med* 2016;51:23-32.
- Lipstein EA, Perrin JM, Kuhlthau KA. School absenteeism, health status, and health care utilization among children with asthma: associations with parental chronic disease. *Pediatrics* 2009;123:e60-6.
- Bener A, Kamal M, Shanks NJ. Impact of asthma and air pollution on school attendance of primary school children: are they at increased risk of school absenteeism? *J Asthma* 2007;44:249-52.
- Gait L, Hepworth C, Lilley A, et al. Experiences of participating in a new integrated programme of asthma care: patients and parents' perspectives. *Eur Respir J* 2019;54.
- Dick S, Friend A, Dwyer K, et al. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. *BMJ Open* 2014;4:e006554.
- Dick S, Doust E, Cowie H, et al. Associations between environmental exposures and asthma control and exacerbations in young children: a systematic review. *BMJ Open* 2014;4:e003827.
- van de Loo KFE, van Gelder MMHJ, Roukema J, et al. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *Eur Respir J* 2016;47:133-46.
- Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;129:735-44.
- Silvestri M, Franchi S, Pistorio A, et al. Smoke exposure, wheezing, and asthma development: a systematic review and meta-analysis in unselected birth cohorts. *Pediatr Pulmonol* 2015;50:353-62.
- Quansah R, Jaakkola MS, Hugg TT, et al. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. *PLoS One* 2012;7:e47526.
- Jiang D, Wang L, Bai C, et al. Association between abdominal obesity and asthma: a meta-analysis. *Allergy Asthma Clin Immunol* 2019;15:16.
- Mangini LD, Hayward MD, Zhu Y, et al. Timing of household food insecurity exposures and asthma in a cohort of US school-aged children. *BMJ Open* 2018;8:e021683.
- Mangini LD, Hayward MD, Dong YQ, et al. Household food insecurity is associated with childhood asthma. *J Nutr* 2015;145:2756-64.
- King C, Surace AE, Jeffers G, et al. The effects of ambient air pollution on the risk of hospitalisation with acute respiratory illnesses in children: an overview of systematic reviews. *Eur Respir J* 2019;54.
- Hehua Z, Qing C, Shanyan G, et al. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: a systematic review. *Environ Res* 2017;159:519-30.
- Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014;383:1581-92.
- Been JV, Nurmatov UB, Cox B, et al. Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis. *Lancet* 2014;383:1549-60.
- Mackay D, Haw S, Ayres JG, et al. Smoke-Free legislation and hospitalizations for childhood asthma. *N Engl J Med* 2010;363:1139-45.
- Woods ER, Bhaumik U, Sommer SJ, et al. Community asthma initiative: evaluation of a quality improvement program for comprehensive asthma care. *Pediatrics* 2012;129:465-72.
- Braman SS. The global burden of asthma. *Chest* 2006;130:45-12.
- Ferrante G, La Grutta S. The burden of pediatric asthma. *Front Pediatr* 2018;6:186.
- Simba J, Marete I, Whanyenya R, et al. Knowledge and perceptions on childhood asthma among care-takers of children with asthma at a national referral hospital in Western Kenya: a descriptive study. *Afr Health Sci* 2018;18:965-71.
- Dimitri P. Child health technology: shaping the future of paediatrics and child health and improving NHS productivity. *Arch Dis Child* 2019;104:184-8.
- Jeminiwa R, Hohmann L, Qian J, et al. Impact of eHealth on medication adherence among patients with asthma: a systematic review and meta-analysis. *Respir Med* 2019;149:59-68.
- Bian J, Guo Y, Xie M, et al. Exploring the association between self-reported asthma impact and Fitbit-Derived sleep quality and physical activity measures in adolescents. *JMIR UHealth* 2017;5:e105.
- Bian J, Cristaldi KK, Summer AP, et al. Association of a school-based, Asthma-Focused telehealth program with emergency department visits among children enrolled in South Carolina Medicaid. *JAMA Pediatr* 2019;173:1041-8.
- Bloom CJ, Nissen E, Douglas JJ, et al. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018;73:313-20.
- Kocis O, Lalos A, Arvanitis G, et al. Multi-model short-term prediction schema for mHealth empowering asthma self-management. *Electron Notes Theor Comput Sci* 2019;343:3-17.

ARTIGO ORIGINAL INVESTIGAÇÃO

Modelo de estratificação do risco de cancro de pulmão do *Liverpool Lung Project*: calibração e validação prospetiva

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RESUMO

Contexto A deteção precoce do cancro do pulmão salva vidas, como demonstrado pelos dois maiores ensaios de rastreio por TAC de dose reduzida publicados. A sua implementação ótima depende da nossa capacidade de identificar os indivíduos em maior risco.

Métodos A versão 2 da pontuação de risco do *Liverpool Lung Project* (LLPv2) foi desenvolvida a partir de dados de caso-controlo em Liverpool e posteriormente adaptada quando aplicada à seleção de indivíduos para o ensaio de rastreio do pulmão do Reino Unido. O objetivo foi produzir a versão 3 (LLPv3) do modelo por meio de calibração a números nacionais de 2017. Validámos tanto a LLPv2 como a LLPv3 utilizando dados de questionários de 75 958 indivíduos, cuja doença foi acompanhada ao longo de 5 anos. Validámos tanto a discriminação, utilizando a análise da curva da característica operacional do receptor (ROC), como a incidência absoluta, comparando os decis da incidência prevista com a incidência observada. Calculámos a diferença proporcional enquanto percentagem de excesso ou défice de cancros observados em comparação com os previstos. Também realizámos testes Hosmer-Lemeshow.

Resultados Foram diagnosticados 599 cancros do pulmão ao longo de 5 anos. A discriminação de LLPv2 e LLPv3 foi significativa, com uma área sob a curva ROC de 0,81 (95% IC 0,79 a 0,82). No entanto, a LLPv2 sobrestimou o risco absoluto na população. A diferença proporcional foi de -58,3% (95% IC -61,6% a -54,8%), ou seja, o número real de cancros foi apenas 42% do número previsto. Na LLPv3, calibrada para valores nacionais de 2017, a diferença proporcional foi de -22,0% (95% IC -28,1% a -15,5%).

Conclusões Enquanto a LLPv2 e a LLPv3 têm o mesmo poder discriminatório, a LLPv3 melhora a previsão absoluta do risco de cancro do pulmão e deve ser considerada para utilização em estudos de implementação futuros no Reino Unido.

INTRODUCTION

Evidence from randomised trials estimates a significant 20% reduction in lung cancer mortality with invitation to low-dose CT screening.^{1,2} In the USA, lung cancer screening has been recommended by the United States Preventive Services Task Force (USPSTF) and in other countries there are a growing number of implementation studies aimed at addressing outstanding pragmatic issues of wider roll out for national programmes. An issue of fundamental importance is identification of a population at sufficient risk of disease to optimise detection in those who would benefit from screening for lung cancer, minimise unnecessary investigations for those at low risk and provide a cost-effective programme. While there is ample evidence on the discriminatory power of various risk prediction tools, there is a need to validate these tools on prospectively collected data to estimate their predictive power, as recommended by Toll *et al*³ and as performed by Ten Haaf *et al*.⁴

The Liverpool Lung Project risk model (LLPv2) was developed on a case-control study in Liverpool and provides a percentage risk score

Key messages

What is the key question?

► The Liverpool Lung Project risk model (LLPv2) has been developed to identify those at high risk of lung cancer for intervention (eg, by lowdose CT in the UK Lung Screening Trial), here we assess the discriminatory and predictive power of the risk model and propose an updated version (LLPv3) more suitable for a contemporary country-wide population.

What is the bottom line?

► The LLPv2 risk model was validated with a significant discriminatory power, but overestimates risk compared with the improved LLPv3.

Why read on?

► This study identifies differences in the rition control and occupational health policy.

for an individual over the next 5 years, based on questionnaire data.⁵ It has been validated in three international data sets and had an area under the curve (AUC) of 0.82 in the UK Cohort.⁶ It was later amended (LLPv2) due to observations in the UK Lung Screening (UKLS) Trial^{7,8} in which it was used to select subjects for low-dose CT screening. In this paper, we report on further amendments to the model (LLPv3) calibrated to the whole of England and to more recently available lung cancer incidence data, with prospective validation in a large cohort covering two regions of England.

METHODS

Development and calibration

The LLP risk model was derived from data relating to 579 individuals with lung cancer and 1157 controls, recruited between 1998 and 2005 in an area of North West England. Variables included in the model were age, sex, cigarette smoking history, prior diagnosis of pneumonia, occupational exposure to asbestos, prior diagnosis of malignant tumour and family history of lung cancer. The model development process and internal validation have been published elsewhere.⁵

A second version of the model (LLPv2) was subsequently developed, following observations in the UKLS that resulted in changes to two variables: previous diagnoses of other lung diseases were considered alongside pneumonia, and cigar and pipe smoking were included alongside cigarettes⁸ in the UKLS Questionnaire (online supplemental material 1). The change was prompted by the observation in UKLS that those included on the basis of duration of use of other smoking materials had at least the prevalence of lung cancer as those included with the same



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duration of cigarette smoking.⁷ The numerical parameters of the model remained unchanged. Model formulation is given in online supplemental material 2. The LLP risk models only use smoking duration, as in common with others,^{9–11} we found this to be the strongest predictor of the various smoking metrics, and other aspects such as amount smoked were not significant when adjusting for duration.⁴

The age-standardised incidence ratio for lung cancer in Liverpool compared with England as a whole for the years 2012–2016 was 1.86.¹² The age-standardised rates of newly diagnosed cases of lung cancer for England were 101.4 per 100000 of population for men in 2006 and 57.9 for women; the corresponding rates in 2017 (the most recent year for which these data were available) were 86.8 and 67.0, respectively.¹³ In order to produce an updated version of the model (LLPv3) for current use in the UK, the age-related risk factors in the model were each adjusted to approximate the effect of reducing the calculated risk score by a factor of $1.86 \times 101.4 / 86.8$ for men and $1.86 \times 57.9 / 67.0$ for women, in the absence of any other risk factors (see online supplemental material 2).

Validation

Participants for the UKLS were recruited from people aged 50–75 (at the time of initial approach) living in the areas covered by six Primary Care Trusts in two regions of the UK (North West England and East of England), by means of a questionnaire sent to just under a quarter of a million people. Recruitment methods and participant rates for UKLS have been reported elsewhere.⁸

Of the 75958 people who expressed an interest in participating in the study (by completing and returning the questionnaire between September 2011 and March 2013), 8729 were assessed to have a high-risk score (estimated 5% risk or higher over 5 years) for lung cancer. After exclusions, 4061 gave informed consent for low-dose CT randomisation and biosample provision. Of these, 2028 were randomised to the CT screening arm (intervention) and 2027 to the non-screening arm (control); the remaining 6 were not randomised.

The questionnaire sent out as part of the initial approach for recruitment to the trial used a standardised format (see online supplemental material 1) and covered personal history of non-malignant lung diseases, previous malignancy, exposure to asbestos, family history of lung and other cancers, and smoking history. For all those who had ever smoked regularly, questions covered the type of smoking material, quantity and the age of starting and (if applicable) stopping smoking. For validation of the amended model (LLPv3), we used prospective data for the 75958 people who returned the initial questionnaire. Coding and interpretation details are given in online supplemental material 3.

Cancer and death registration data between 2011 and 2018 were obtained from Public Health England (PHE) and linked through NHS number by a third party to the research cohort (PHE Office of Data Release study 1819_074). This provided the minimum of 5 years of follow-up required for testing the LLP model. Only diagnoses within the first 5 years were taken into account.

A risk score representing cancer risk over 5 years was calculated for each individual from the questionnaire data using both LLPv2 and LLPv3. The input variables were derived according to the algorithms shown in the online supplemental material.

A receiver operating characteristic (ROC) curve was plotted to assess the ability of the model to successfully distinguish between those persons who went on to develop lung cancer and those who did not. The ROC curve is a plot of the true positive rate (or sensitivity) against the false positive rate (1–specificity) for different risk scores. The AUC was calculated, along with the corresponding 95% CI.

Individuals allocated to the intervention arm of the UKLS trial, nested within the validation cohort, may have potentially received additional diagnostic procedures in the form of low-dose CT scans, compared with the rest of the study population.

In order to investigate the possible impact of this, sensitivity analysis was carried out, excluding this subgroup. In order to assess the calibration of the predictive model, we ranked the LLPv3 risk scores, assigned decile groups and carried out a linear regression of the log-odds ($f(x) = \log_e \frac{x}{1-x}$) of the rate of observed cancers in each group against the log-odds of the mean of the risk scores in the

group. The proportionate difference (the number of cancers observed in excess or deficit of those that would have been expected based on the risk scores, divided by that expected number) was also calculated. In addition, we carried out Hosmer–Lemeshow tests, with the population classified by predicted risk deciles.¹⁴ However, interpretation of these has to be qualified by the test's sensitivity to categorisation, sample size and ties.^{15–17}

Statistical analyses were performed using STATA, V.15.1 (StataCorp).

RESULTS

Table 1 shows the basic demographic and risk profile of the study population, and of the subgroup developing lung cancer. Overall, almost half the population were men, 65% were aged 60 years or over, 18% were in the most deprived index of multiple deprivation (IMD) quintile and more than half the population had smoked at some time in their lives. As expected, the lung cancer cases were older, had higher rates of smoking and were more deprived than the overall population.

Lung cancers were diagnosed in a total of 599 people over the period of follow-up (5 years from the questionnaire completion date), that is, 0.8% of the study population. Table 2 shows the number of cancers that were potentially detectable, that is, occurring in subjects who qualify for surveillance and those occurring in subjects who do not qualify using the amended LLP model (assuming 100% sensitivity of CT screening) for selected referral thresholds. The table also shows the corresponding sensitivity and specificity of exceeding the threshold. Results are given for men and women separately, and overall. Under LLPv2, a threshold of 3.7% would have yielded 10864 subjects qualifying. The equivalent threshold under LLPv3 would be 2.0%. The numbers needed to screen (with the risk model) per cancer potentially detectable, fall from 62 with a 0.5% LLPv3 threshold to 21 with a 4.5% threshold. The positive likelihood ratios increased from 2.0 at the LLPv3 0.5% threshold to 6.3 at the 4.5% threshold. The corresponding ranges for men only were 1.9–5.4 and for women 2.3–7.8.

The ROC curve for LLPv3 is given in figure 1. The curves for LLPv2 and LLPv3 are almost identical, as would be expected, since the coefficients pertaining to the risk factors are the same, and the ranking of most individuals is unchanged from version 2 to version 3. As a result, the discrimination is very similar. The AUC in each case was 0.81 (95% CI 0.79 to 0.82). After excluding individuals allocated to the UKLS trial intervention arm, the AUC and 95% CI were also unchanged.

The numbers of cancers detected by LLP decile groups and the expected numbers of cancers in each group are given in table 3, for both LLPv2 and LLPv3. Corresponding figures separately for men and women are given in online supplemental material 4. The increasing actual risk with predicted risk can be seen from the increasing percentage of cancers in successive risk deciles. The 10% of subjects in the second decile of predicted risk by LLPv3 contribute 2% (12/599) of the cancers whereas the 10% in the sixth decile contribute 4% (24/599) and the 10% in the highest decile contribute 45% (269/599).

Figure 2 shows the log odds of the observed rate of cancers (with 95% CIs) plotted against the log odds of the mean risk score for both LLPv2 and LLPv3.

For LLPv2, the slope of the calibration line was 0.88 (95% CI 0.74 to 1.02), and the intercept at the origin (corresponding to a risk score of 50%) was –1.31 (95% CI –1.96 to –0.66). The orange line represents perfect agreement between observed and expected cancers, indicating that the LLPv2 model overestimated the risk. The proportionate difference was $(599 - 1436) / 1436$ or –58.3% (95% CI –61.6% to –54.8%).

For LLPv3, the slope was largely unchanged at 0.90 (95% CI 0.75 to 1.05), the intercept at the origin was –0.66 (95% CI –1.46 to 0.15), and the proximity to the orange line indicates reduced discrepancy between observed and expected cancers.

There was still a tendency to overestimate the number of cancers, especially at the highest risk levels, but the proportionate difference was considerably lower, at –22.0%.

Table 1 Baseline factors and lung cancers diagnosed

	All participants (%)		Participants diagnosed with lung cancer within 5 years (%)		Cumulative incidence per 1000 of lung cancer over 5 years
All participants	75 958		599		7.9
Sex					
Male	37 525	(49.4)	327	(54.6)	8.7
Female	38 433	(50.6)	272	(45.4)	7.1
Age					
50–54	12 123	(16.0)	21	(3.5)	1.7
55–59	14 359	(18.9)	54	(9.0)	3.8
60–64	19 007	(25.0)	148	(24.7)	7.8
65–69	19 602	(25.8)	224	(37.4)	11.4
70–74	9993	(13.2)	134	(22.4)	13.4
75–79	874	(1.2)	18	(3.0)	20.6
Region					
North West England	32 609	(42.9)	332	(55.4)	10.2
East of England	43 349	(57.1)	267	(44.6)	6.2
IMD quintile					
1 (most deprived)	13 893	(18.3)	214	(35.7)	15.4
2	9813	(12.9)	92	(15.4)	9.4
3	13 337	(17.6)	102	(17.0)	7.6
4	16 707	(22.0)	77	(12.9)	4.6
5 (least deprived)	22 198	(29.2)	114	(19.0)	5.1
Unknown	10	(-)	–	(-)	–
Smoking duration					
Never	35 535	(46.8)	58	(9.7)	1.6
1–19 years	10 889	(14.3)	29	(4.8)	2.7
20–39 years	19 284	(25.4)	208	(34.7)	10.8
40–59 years	10 204	(13.4)	302	(50.4)	29.6
60 years or more	46	(0.1)	2	(0.3)	43.5
History of pneumonia or other lung conditions					
No	57 558	(75.8)	351	(58.6)	6.1
Yes	18 400	(24.2)	248	(41.4)	13.5
Personal history of cancer					
No	66 855	(88.0)	493	(82.3)	7.4
Yes	9103	(12.0)	106	(17.7)	11.6
Asbestos exposure					
No	64 796	(85.3)	471	(78.6)	7.3
Yes	11 162	(14.7)	128	(21.4)	11.5
Family history of lung cancer					
None	63 321	(83.4)	453	(75.6)	7.2
Early onset (before age 60)	4532	(6.0)	77	(12.9)	17.0
Late onset (on or after age 60)	8105	(10.7)	69	(11.5)	

Figure 3 shows the corresponding graphs for LLPv3 for men and women separately. The slope for men was 0.89 (95% CI 0.79 to 0.99) and the intercept was –0.74 (95% CI –1.28 to –0.21). For women, there was stronger agreement between predicted and observed numbers, with a slope of 0.93 (95% CI 0.72 to 1.14) and an intercept of 0.47 (95% CI –1.6 to +0.65).

The corresponding Hosmer-Lemeshow tests yielded a χ^2 of 530.06 ($p < 0.001$) for LLPv2 overall, with 437.78 ($p < 0.001$) for males and 110.18 ($p < 0.001$) for women. For LLPv3, a considerably improved fit was shown, with the Hosmer-Lemeshow statistics reduced by a factor of 10, with χ^2 statistics of 50.87 ($p < 0.001$) overall, 43.82 ($p < 0.001$) for men and 15.19 ($p = 0.06$) for women. In the figures for LLPv3, overall and men only, 65% and 73%, respectively, of the χ^2 figures were contributed by the highest decile. This can also be seen in table 3 and online supplemental material 4.

DISCUSSION

We present an updated version of the LLP model (LLPv3) designed to assess risk of lung cancer in the next 5 years for the contemporaneous English population. Its primary intended use is to identify people who might benefit from lung cancer screening. We recalibrated the LLPv2 model used in the UKLS trial of lung cancer screening taking account of changes to the age-specific and sex-specific lung cancer risk profile of England and the difference in risk between the Liverpool area and England as a whole. We prospectively validated

the LLP model by using baseline risk factors and follow-up of lung cancer diagnoses in a large cohort (>75000) of individuals expressing interest in the UKLS study. This demonstrated excellent discrimination based on an AUC measure of 0.81 (95% CI 0.79 to 0.82) for both LLPv2 and the updated LLPv3. The newer model also provided a very good estimation of future risk through comparison of observed and expected lung cancer outcomes.

However, without the calibration to the current England population in terms of age-specific and sex-specific lung cancer risk, there would have been considerable overestimation of risk. This is consistent with the findings of Katki *et al.*,¹⁸ who concluded that previous versions of the LLP model overestimated future incidence.

Risk-based lung cancer screening strategies prevent significantly more lung cancer deaths than the current the USPSTF recommendations on lung cancer screening,¹⁹ which is currently the only internationally approved government stratification system and is also supported by the USA medical care agency (Medicare).^{20–23} Two lung cancer risk prediction models have been previously used in lung cancer CT screening clinical trials, the PanCan risk model (precursor to the PLCO_{M2012} model), in the PanCan cohort CT trial²⁴ and the LLPv2 in the UKLS trial.⁸ The PanCan model did show good overall discrimination; however, it underestimated the observed risk of lung cancer by 30%. The authors tested both the PanCan and the PLCO_{M2012} in the PLCO trial ‘ever smokers’ and found small differences in the overall prediction, discrimination and calibration.²⁴ A

Table 2 Sensitivity and specificity by LLPv3 5-year risk threshold

LLPv3 risk score referral threshold	Participants with score at least equal to threshold	Cancers potentially detectable	Cancers not detectable	Number needed to screen per cancer potentially detectable	Sensitivity of threshold (%)	Specificity of threshold (%)	LLPv2 equivalent referral threshold* (%)
(a) Males only							
0.5%	18 190	293	34	62	89.6	51.9	1.08
1%	11 694	256	71	46	78.3	69.3	2.15
1.5%	8683	225	102	39	68.8	77.3	3.21
2%	6712	194	133	35	59.3	82.5	4.25
2.5%	5140	168	159	31	51.4	86.6	5.31
3%	4022	143	184	28	43.7	89.6	6.32
4.5%	2104	95	232	22	29.1	94.6	9.32
(b) Females only							
0.5%	14 347	228	44	63	83.8	63.0	0.79
1%	8333	197	75	42	72.4	78.7	1.59
1.5%	5425	162	110	33	59.6	86.2	2.37
2%	4152	135	137	31	49.6	89.5	3.15
2.5%	2992	114	158	26	41.9	92.5	3.94
3%	2340	99	173	24	36.4	94.1	4.73
4.5%	1079	57	215	19	21.0	97.3	7.00
(c) All subjects							
0.5%	32 537	521	78	62	87.0	57.5	0.90
1%	20 027	453	146	44	75.6	75.0	1.86
1.5%	14 108	387	212	36	64.6	81.8	2.89
2%	10 864	329	270	33	54.9	86.0	3.70
2.5%	8132	282	317	29	47.1	89.6	4.78
3%	6362	242	357	26	40.4	91.9	5.60
4.5%	3183	152	447	21	25.4	96.0	8.65

*To achieve at least as many referrals.

LLPv2, Version 2 of the Liverpool Lung Project risk score.

number of other lung cancer risk models have been developed and although some have been tested in previously recruited National Lung Screening Trial (NLST) subjects and a subgroup of the PLCO population, none have been used as the basis for eligibility in the clinical trial environment.⁴

The UKLS was a pilot CT screening trial and a pragmatic decision was made to select individuals with a 5% predicted risk of developing lung cancer over a 5-year period, in order to ensure the trial had a large number of lung cancers. This objective was successfully achieved, as 2.2% of subjects with lung cancer were identified in the baseline screen, which was significantly higher than either the NLST¹ or NELSON² trials. It was acknowledged that the risk cut-off might be lower in a large national screening programme.²⁵

The discriminatory power of the LLPv2 was significant with an AUC of 0.81; however, the model was found to overestimate the absolute risk approximately twofold. The LLP risk model was based on a very high-risk population recruited between 1997 and

2005 in the NW of England and the incidence rates for lung cancer included in the model were based on 2007 data.

On calibrating the age-specific and gender-specific intercepts to the current English data,^{12,13} a recalibrated LLP risk model is now provided here (LLPv3 risk model). As the calibration was independent of the data available from the UKLS study, we were able to use that to validate the model. The recalibrated LLPv3 model demonstrated a significantly improved absolute prediction with the expected rates of cancer in the population, as demonstrated by the correlation between the risk score and the observed cancer rates.

While the prediction as measured by the Hosmer-Lemeshow test is not perfect, we note the reservations about this test specified above. We also note that the LLPv3 clearly predicts better for women than for men, and that the only substantial departure of observed from predicted numbers is in one extreme category, the highest decile of risk, and in males only.

We acknowledge there are a number of limitations; however, many are shared by similar risk model studies. First, the study population, although large at 75 958, represents a self-selecting group from 247354 individuals (30.7%) approached for the UKLS trial. Potentially, there is over-representation of lower risk, better educated, 'worried well' individuals (often associated with higher socioeconomic groups).²⁶ On examining the UKLS IMD quintiles, the two least deprived (51.2%) outnumber the two most deprived (31.2%); however, it should be acknowledged that the LLP risk score is predictive across all IMD quintiles and a similar IMD profile would be expected on the introduction of national screening. There is a recognition that more should be done to target the 'hard to reach' individuals in lower socioeconomic groups, who have higher rates of lung cancer (as confirmed here: most deprived quintile 15.4 per 1000 in 5 years, least deprived 5.1). Second, the UKLS study population represents a limited geographical subpopulation of the UK (both in the North West and the East of England), and one of the areas overlaps considerably with the area supplying the original estimation dataset.

However, no individual appears in both estimation and validation sets, and the validation set appears to be broadly representative as demonstrated by the fit achieved for risk calibrated to data for England as a whole. This highlights that basing a risk score on a defined region (ie, Liverpool) one may overestimate lung can-

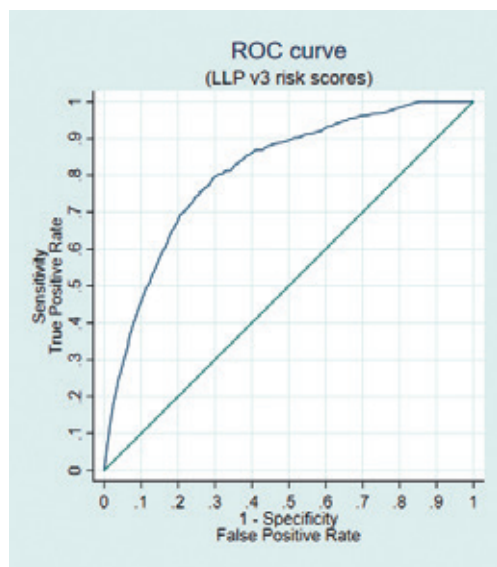
**Figure 1** Receiver operating characteristic (ROC) curve for Version 3 of the Liverpool Lung Project risk score (LLPv3).

Table 3 Risk score ranges and observed and expected lung cancers by risk decile for Version 2 of the Liverpool Lung Project risk score (LLPv2) and Version 3 of the Liverpool Lung Project risk score (LLPv3)

Decile	LLPv2				LLPv3			
	Size of decile group*	Range of risk score (%)	Number of cancers observed (%)	Expected number of cancers	Size of decile group*	Range of risk score (%)	Number of cancers observed (%)	Expected number of cancers
1 (lowest risk)	7790	0.06–0.17	0 (0)	10	8457	0.03–0.10	0	6
2	7928	0.18–0.27	12 (2)	18	7541	0.11–0.15	12 (2)	10
3	7180	0.28–0.38	12 (2)	23	6807	0.16–0.20	11 (2)	12
4	7521	0.39–0.49	20 (3)	33	8284	0.21–0.28	25 (4)	20
5	7622	0.50–0.69	20 (3)	45	7042	0.29–0.37	16 (3)	23
6	7562	0.70–1.00	20 (3)	64	7887	0.38–0.56	24 (4)	37
7	7614	1.01–1.61	49 (8)	97	7154	0.57–0.82	36 (6)	49
8	7555	1.62–2.63	72 (12)	152	7747	0.83–1.39	76 (13)	84
9	7687	2.64–5.08	131 (22)	283	7500	1.40–2.64	130 (22)	145
10 (highest risk)	7499	5.09–53.71	263 (44)	711	7539	2.65–34.72	269 (45)	382
All	75 958		599	1436	75 958		599	768

*These are not equal, since individuals were allocated to groups by an algorithm which ensure all those with the same score were assigned to the same group.

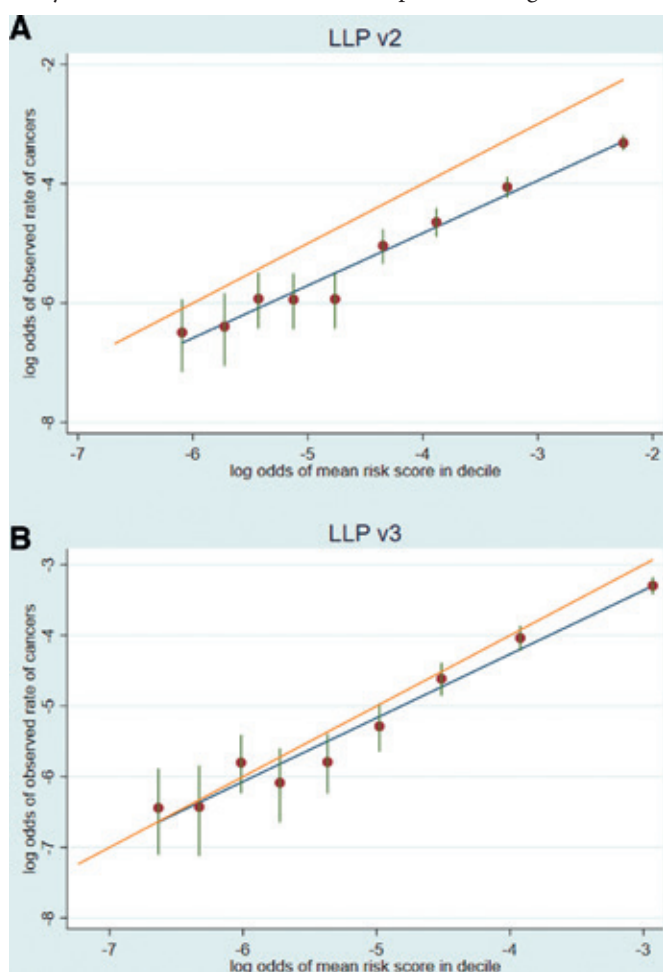
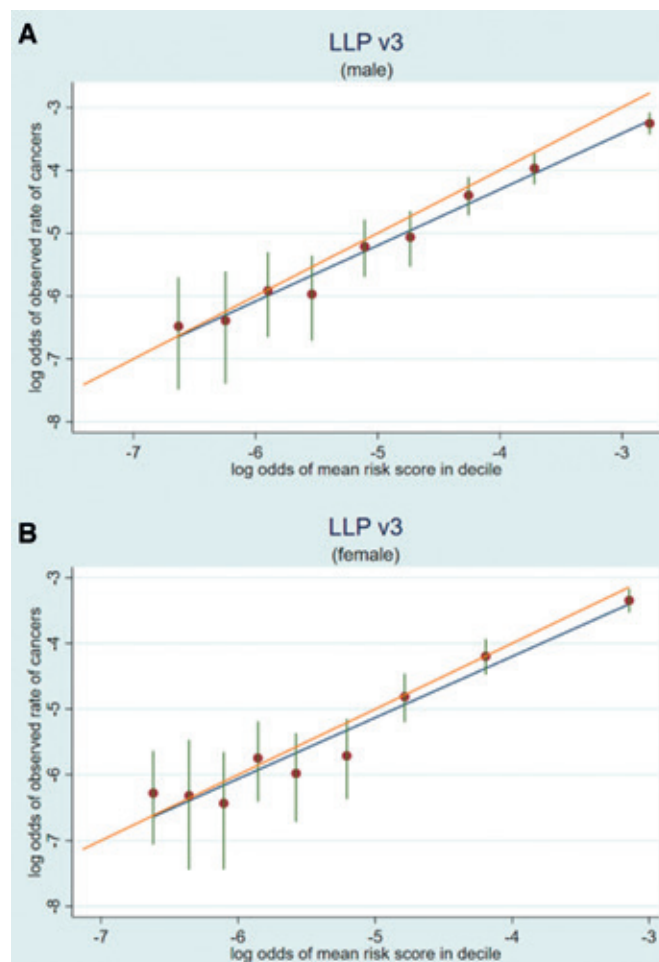
cer risk if that region has a higher incidence than the rest of the country. When extrapolating risk models from smaller studies in defined regions, we therefore recommend that this is taken into account.

In terms of discrimination, previous retrospective validation exercises on LLPv2 have shown a range of discriminatory capacities, with AUCs ranging from 0.67 to 0.82.⁶ However, the lower figure pertains to a cohort undergoing surgery, which would not necessarily be representative of lung cancer cases as a whole.

Primary care data are usually not sufficient to supply the risk factors in this model, or in most other lung cancer risk models.¹⁸ The paradigm for selection of individuals for additional lung cancer surveillance or prevention is to use a crude risk criterion such as ever smoking to select candidates from primary care, then carry out a formal risk assessment as part of a lung health check

on those candidates using a tool such as one of the LLP or PLCO models. This has been used in the Lung Screen Uptake Trial,²⁷ the Yorkshire Lung Screening Trial,²⁸ and the Manchester²⁹ and Liverpool³⁰ demonstration projects.

We note here that the LLPv2 and LLPv3 are essentially aimed at risk of lung cancer in the next 5 years. They are not diagnostic tests for lung cancer. As such, the positive likelihood ratios are low in comparison with some diagnostic tests. The clinical utility of our preferred risk tool LLPv3 will depend on what intervention might be triggered by a given risk level. The most obvious intervention would be surveillance with low-dose CT, but this need not be the only response to lung cancer risk. In this paper, therefore, we have concentrated on accuracy of the prediction, and have not introduced further dimensions such as clinical or public preference. Detailed clinical implications of different risk thresholds using LLPv3 will be the subject of a future paper. This will likely include

**Figure 2** Observed versus predicted log odds of cancer for Version 2 of the Liverpool Lung Project risk score (LLPv2) and Version 3 of the Liverpool Lung Project risk score (LLPv3).**Figure 3** Observed versus predicted log odds of cancer for Version 3 of the Liverpool Lung Project risk score (LLPv3) (A) men; (B) women.

Decision Curve Analysis and possibly other tools such as Mean Risk Stratification and Incremental Net Benefit.^{31–33}

The LLPv2 and PLCO_{m2012} have been used and initial data published in three UK lung cancer early detection/CT screening implementation projects, the Liverpool Healthy Lung Programme (LLPv2),³⁰ the Lung Screen Uptake Trial,²⁷ and the West London Lung Cancer Screening pilot (WLLCS).³⁴ All three of these projects successfully selecting high-risk patients and identified early stage lung cancers. The Yorkshire Lung Screening trial²⁸ has also used the LLP v2 and PLCO_{m2012} risk models; however, the results have not as yet been published.

The WLLCS pilot has published its baseline data on both the LLPv2 and PLCO_{m2012} risk models. The authors reported that 1159 participants were eligible for a CT scan, of which 451/1159 (38.9 %) had a LLPv2 $\geq 2.0\%$; only 71/1159 (6.1 %) had a PLCO_{m2012} $\geq 1.5\%$, lung cancer was detected in 29/1145 (2.5 %) participants scanned 5/29 participants with lung cancer did not meet a PLCO_{m2012} threshold of $\geq 1.51\%$; however, all had a LLP v2 $\geq 2.0\%$.

The Manchester Health Lung Check (MLHC) selected patients for their study with the PLCO_{m2012} risk model. They have recently analysed the performance of both the LLPv2 and PLCO_{m2012} models in their data set,³⁵ using $\geq 2.5\%$ LLPv2 risk model and $>1.51\%$ risk calculated from the PLCO_{m2012} model.

In the MLHC 1430 dataset, the authors calculated that 93.5% (58 of the 62 identified) of the lung cancer cases would have been identified by the LLPv2 $\geq 2.5\%$ risk; with a further 272 participants who would have been eligible with LLPv2 but ineligible with PLCO_{m2012}² however, the outcome of these individuals was unknown.

An international comprehensive analysis of seven lung cancer risk models, (including LLPv1) has been undertaken using data from the PLCO and NLST data sets.⁴ However, a number of the LLPv1 parameters were not available; asbestos exposure, nor history of pneumonia, nor the age of diagnosis of the first degree relatives' family history of lung cancer in the PLCO and NLST datasets. Ten Haaf and coauthors reported that all the seven risk models outperformed the NLST trial eligibility criteria over a wide range of risk thresholds in decision curve analysis, with a higher sensitivity for all models and a slightly higher specificity for a number of the models. The PLCO_{m2012} outperformed all of the models in their analysis and both the LLPv1 and the authors' simplified LLP risk model did not perform as well, overestimating the risk. However, the validation exercise used the LLPv1 model and three of the risk parameters were not available in their test sets.

Given that a likely application for lung cancer risk models such as LLPv3 is determination of eligibility for low-dose CT screening for lung cancer, it is worth remarking that there is a trade-off between potential increases in cost effectiveness with higher risk thresholds and likely comorbidities, which may either impair eligibility for potentially curative surgery in those detected with lung cancer, or otherwise shorten expected life and thus diminish the potential benefits of screening. See Rivera *et al*, for a thorough exegesis of this issue.³⁶

This current analysis provides evidence that the LLPv2 and LLPv3 have the same discriminatory power, but the LLPv3 is now recommended for future UK lung cancer CT screening programmes, as it better estimates the absolute lung cancer risk.

The NHS England 'Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography' protocol³⁷ has included the use of the PLCO_{m2012} (at a 1.5% risk cut-off) and the LLPv2 (at 2.5% risk cut-off). It is now recommended that NHS England use the LLPv3, which is calibrated to sex-specific and age-specific incidence for the whole of England in 2017; a LLPv2 cut-off of 2.5% equates to a risk cut-off of 1.33% over 5 years for LLPv3, so it is in line with the PLCO_{m2012} of $>1.5\%$ over 6 years. To ensure a substantially enhanced risk group, it might be prudent to use a 2.5% threshold using LLPv3 (see table 2).

In conclusion, discrimination of LLPv2 and LLPv3 was excellent. LLPv3, which was calibrated to contemporary, English incidence, achieved more accurate prediction of absolute incidence, and would be more effective in selecting a high-risk group for surveillance in England today.

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Contributors JF: trial conception and design, data interpretation and manuscript review. SWD: trial design, statistical analysis, data interpretation, manuscript review. DV: risk modelling, statistical analysis, data interpretation, manuscript review. MPAD and RG: data interpretation, manuscript review.

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Data availability statement Data are available upon reasonable request. We are committed, in principle, to data sharing with fellow researchers, and are currently drawing up operating procedures for this. We anticipate that the data will be stored securely in Liverpool and reasonable requests for data for further research will be accommodated, subject to compliance with regulations, maintaining the integrity of information governance, and ensuring no loss of confidentiality on the part of the participants of the study. Requests that require considerable data manipulation and management on our part will need to be resourced by those requesting data.

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REFERENCES

- National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomography screening. *N Engl J Med* 2011;365:395–409.
- de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 2020;382:503–13.
- Toll DB, Janssen KJM, Vergouwe Y, et al. Validation, updating and impact of clinical prediction rules: a review. *J Clin Epidemiol* 2008;61:1085–94.
- Ten Haaf K, Jeon J, Tammemägi MC, et al. Risk prediction models for selection of lung cancer screening candidates: a retrospective validation study. *PLoS Med* 2017;14:e1002277.
- Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. *Raj J Cancer* 2008;98:270–6.
- Raji OY, Duffy SW, Agbaje OF, et al. Predictive accuracy of the Liverpool lung project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. *Ann Intern Med* 2012;157:242–50.
- Field JK, Duffy SW, Baldwin DR, et al. UK lung cancer RCT pilot screening trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax* 2016;71:161–70.
- Field JK, Duffy SW, Baldwin DR, et al. The UK lung cancer screening trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess* 2016;20:1–146.
- International Agency for Research on Cancer (IARC). Tobacco smoking and tobacco smoke, 2002. Available: <http://www.inchem.org/documents/iarc/vol83/01-smoking.html> [Accessed 7 Aug 2020].
- Remen T, Pintos J, Abrahamowicz M, et al. Risk of lung cancer in relation to various metrics of smoking history: a case-control study in Montreal. *BMC Cancer* 2018;18:1275.
- Haws L, Haws BT. Aerodigestive cancers: lung cancer. *FP Essent* 2014;424:32–47.
- Public Health England. Public Health Profiles 2020 [Incidence of lung cancer, standardised incidence ratio (Liverpool CCG)]. Available: <https://fingertips.phe.org.uk/local-healthpage/9/gid/1938133184/pat/46/par/E39000026/ati/154/er/E38000101/aid/93237/age/1/sex/4> [Accessed 3 Apr 2020].
- Office for National Statistics. Cancer registration statistics 2019 [Table 8: Directly age-standardised rates per 100,000 population of newly diagnosed cases of cancer (third digit): site and sex, England 1995 to 2017. Available: <https://www.ons.gov.uk/peop lepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancer-registration-statistics-cancer-registration-statistics-england> [Accessed 3 Apr 2020].
- Hosmer DW, Lemeshow S, Sturdivant RX. Applied logistic regression. 3rd ed. New York: Wiley, 2013.
- Kramer AA, Zimmerman JE. Assessing the calibration of mortality benchmarks in critical care: the Hosmer-Lemeshow test revisited. *Crit Care Med* 2007;35:2052–6.
- Kuss O. Global goodness-of-fit tests in logistic regression with sparse data. *Stat Med* 2002;21:3789–801.
- Bertolini G, D'Amico R, Nardi D, et al. One model, several results: the paradox of the Hosmer-Lemeshow goodness-of-fit test for the logistic regression model. *J Epidemiol Biostat* 2006;5:251–3.
- Katki HA, Kovalchik SA, Petito LC, et al. Implications of nine risk prediction models for selecting Ever-Smokers for computed tomography lung cancer screening. *Ann Intern Med* 2018;169:10–19.
- de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. preventive services Task force. *Ann Intern Med* 2014;160:311–20.
- Moyer VA, Force U, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. preventive services Task force recommendation statement. *Ann Intern Med* 2014;160:330–38.
- Centers for Medicare & Medicaid Services. Decision MEMO for screening for lung cancer with low dose computed tomography (LDCT) (CAG-00439N). Available: <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAid=274>
- Field JK, Aberle DR, Altorki N, et al. The International association study lung cancer (IASLC) strategic screening Advisory Committee (SSAC) response to the USPSTF recommendations. *J Thorac Oncol* 2014;9:141–3.
- Ten Haaf K, Bastani M, Cao P, et al. A comparative modeling analysis of risk-based lung cancer screening strategies. *J Natl Cancer Inst* 2020;112:466–79.
- Tammemägi MC, Schmidt H, Martel S, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. *Lancet Oncol* 2017;18:1523–31.
- Haaf KT, de Koning H, Field J. P2.13-025 selecting the risk cut off for the LLP model. *Journal of Thoracic Oncology* 2017;12:S2174.
- Khadjesari Z, Newbury-Birch D, Murray E, et al. Online health check for reducing alcohol intake among employees: a feasibility study in six workplaces across England. *PLoS One* 2015;10:e0121174.
- Quaife SL, Ruparel M, Dickson JL, et al. Lung screen uptake trial (LSUT): randomized controlled clinical trial testing targeted invitation materials. *Am J Respir Crit Care Med* 2020;201:965–75.
- Gabe R, Callister M, Crosbie PA, et al. The Yorkshire lung screening trial, 2018. Available: <https://abstracts.ncrj.org.uk/abstract/the-yorkshire-lung-screening-trial/>
- Crosbie PA, Balata H, Evison M, et al. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. *Thorax* 2019;74:405–9.
- Ghimire B, Maroni R, Vulkan D, et al. Evaluation of a health service adopting proactive approach to reduce high risk of lung cancer: the Liverpool healthy lung programme. *Lung Cancer* 2019;134:66–71.
- Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006;26:565–74.
- Willan AR, Lin DY. Incremental net benefit in randomized clinical trials. *Stat Med* 2001;20:1563–74.
- Katki HA. Quantifying risk stratification provided by diagnostic tests and risk predictions: comparison to AUC and decision curve analysis. *Stat Med* 2019;38:2943–55.
- Bartlett EC, Kemp SV, Ridge CA, et al. Baseline Results of the West London lung cancer screening pilot study - Impact of mobile scanners and dual risk model utilisation. *Lung Cancer* 2020;148:12–19.
- Leibert MB, Balata H, Evison M, et al. Analysis of lung cancer risk model (PLCOM2012 and LLPv2) performance in a community-based lung cancer screening programme. *Thorax* 2020;75:661–8.
- Rivera MP, Tanner NT, Silvestri GA, et al. Incorporating coexisting chronic illness into decisions about patient selection for lung cancer screening. An official American thoracic Society research statement. *Am J Respir Crit Care Med* 2018;198:e3–13.
- NHS England National Cancer Programme. Targeted screening for lung cancer with low radiation dose computed tomography: standard protocol prepared for the targeted lung health checks programme, 2019. Available: <https://www.england.nhs.uk/wp-content/uploads/2019/02/targeted-lung-health-checks-standard-protocol-v1.pdf> [Accessed 16 Apr 2019].

Sobrevivência a longo prazo após início de ventilação não invasiva domiciliária: um estudo europeu

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RESUMO

Introdução Embora a ventilação não invasiva (VNI) domiciliária seja cada vez mais utilizada no tratamento de doentes com insuficiência ventilatória crônica, existem dados limitados sobre o resultado a longo prazo destes doentes. O nosso objetivo foi informar sobre as populações com VNI domiciliária e o resultado a longo prazo de dois centros europeus.

Métodos Análise de coorte incluindo todos os doentes com VNI domiciliária de dois centros europeus entre 2008 e 2014.

Resultados A VNI domiciliária foi iniciada em 1746 doentes para tratar a insuficiência ventilatória crônica causada por (1) síndrome de hipoventilação da obesidade±apneia obstrutiva do sono (SHO±SAOS) (29,5%); (2) doença neuromuscular (DNM) (22,7%); e (3) doenças obstrutivas das vias aéreas (DOVA) (19,1%). A sobrevivência mediana global após o início da VNI foi de 6,6 anos. A sobrevivência mediana variou pela etiologia subjacente da insuficiência respiratória: DNM de rápida progressão 1,1 anos, DOVA 2,7 anos, SHO±SAOS >7 anos e DNM de lenta progressão >7 anos. A análise multivariada demonstrou uma mortalidade mais elevada em doentes com DNM de rápida progressão (HR 4,78, IC 95% 3,38 a 6,75), DPOC (HR 2,25, IC 95% 1,64 a 3,10), idade >60 anos no início da VNI domiciliária (HR 2,41, IC 95% 1,92 a 3,02) e início da VNI após uma admissão aguda (HR 1,38, IC 95% 1,13 a 1,68). Os fatores associados à menor mortalidade foram a adesão à VNI >4 horas por dia (HR 0,64, 95% IC 0,51 a 0,79), SAOS (HR 0,51, 95% IC 0,31 a 0,84) e sexo feminino (HR 0,79, 95% IC 0,65 a 0,96).

Conclusão A taxa de mortalidade após o início da VNI domiciliária é elevada, mas varia significativamente de acordo com a etiologia subjacente da insuficiência respiratória. Em doentes com insuficiência respiratória crônica, a iniciação da VNI domiciliária após uma admissão aguda e reduzidos níveis de adesão à VNI são características de prognóstico reservado e podem ser objeto de intervenção.

INTRODUCTION

Home non-invasive ventilation (NIV) is widely used for the management of chronic hypercapnic respiratory failure in both Europe¹ and the USA.² While initially used in patients with chronic respiratory failure secondary to neuromuscular disease,³ there are increasing observational and randomised clinical trial data supporting the provision of home NIV in patients with obesity-related respiratory failure^{4,5} and COPD.^{6–8} These data, along with the increasing prevalence of obesity, have led to an expansion in the number of patients established on home NIV.⁹ However, unlike other chronic respiratory diseases such as idiopathic pulmonary fibrosis,¹¹ lung cancer¹² and pulmonary hypertension,¹³ the long-term outcome of patients with chronic hypercapnic respiratory failure treated with home NIV remains unclear. Previous data included patients receiving long-term oxygen and invasive ventilation¹⁴ and lacked generalisability

Key messages

What is the key question?

► What is the long-term outcome of patients treated with home non-invasive ventilation?

What is the bottom line?

► The median survival following initiation of home non-invasive ventilation is 6.6 years.
► Adherence to treatment (>4 hours per night) and elective timing of initiation of home noninvasive ventilation are possible modifiable factors associated with improved survival.

Why read on?

► This study describes home non-invasive ventilation populations at two large European home non-invasive ventilation centres and explores factors associated with mortality.

due to the focus on a specific underlying respiratory disease from single centres.^{15–19} Furthermore, since previous data were published, NIV devices^{20,21} and set-up strategies^{22,23} have evolved, leading to significant changes in clinical practice. The aim of the current study was to report the underlying disease types for patients established on home NIV, the NIV device parameters and the long-term outcome from two European specialist centres.

METHODS

We conducted a cohort analysis of patients set up on home NIV in two specialist centres: one in France and one in the UK.

Population

Patients were prospectively included in administrative databases used for equipment-related purposes in two adult respiratory centres. Medical data and clinical outcome were retrospectively reviewed by selecting all patients who were newly established on home NIV between 2008 and 2014. We excluded all patients set up on CPAP, adaptive servo-ventilation and patients receiving invasive ventilation via tracheostomy. Decision to initiate home NIV was based on a comprehensive clinical and physiological assessment by a senior clinician with experience in home ventilation based on patient symptoms, arterial blood gas and lung function test results. Patient selection was in line with published guidelines, with NIV prescribed for patients with chronic hypercapnic respiratory failure and sleep disordered breathing.

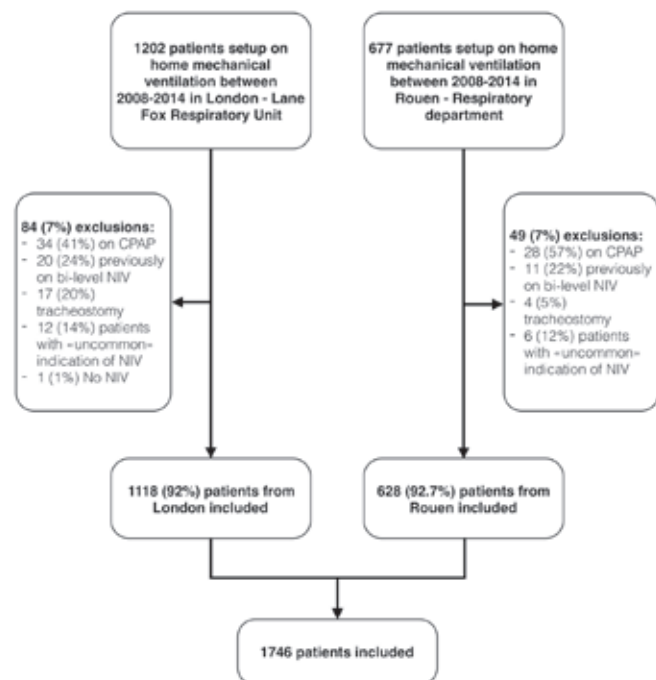


Figure 1 Study population flow chart. CPAP, continuous positive airway pressure, NIV, non-invasive ventilation.

Patients with severe obstructive sleep apnoea and significant residual apnoea-hypopnoea index (>30 per hour) on maximal (20 cmH₂O) CPAP therapy or not tolerant of CPAP or hypercapnic despite CPAP therapy were also established on NIV. Home NIV was established at an inpatient assessment using respiratory polygraphy and/or overnight transcutaneous oximetry and/or morning arterial blood gas according to local established protocols. Overnight titration was performed to treat sleep disordered breathing and manage daytime chronic ventilatory failure. Based on clinical practice, patients were instructed to use their NIV for at least 4 hours per day, but ideally for the full duration of their sleep. Patients with progressive neuromuscular disease were provided with devices with an internal battery and advised to extend use into wakefulness with disease progression.

NIV service

The characteristics of the NIV services and healthcare organisation are described in the online supplementary material.

Ventilator databases

For Rouen, the database was retrieved from ADIR Assistance (Astén Santé, Orvault, France), a healthcare provider that delivers home NIV for Rouen University Hospital. For London, the database was retrieved from Lane Fox Respiratory Service technical ventilator database, which records home NIV set-up for Guy's and St Thomas' NHS Foundation Trust. In both centres technical databases included patients' identification, date of birth, date of home NIV set-up, initial ventilator device and settings, interface, prescribed duration of ventilation, hours of NIV use (adherence), and date of last patient contact. Adherence to NIV was measured using the number of device's blowing hours divided by the number of days following NIV set-up. Changes in settings or interface were not systematically recorded and therefore were not included in the analysis. Patients were followed up until death or censored at the point of last verified health status or loss of contact with home ventilation centre. When applicable, date of cessation of follow-up from the NIV centre was recorded. Reasons for follow-up cessation were classified as follows: (1) death; (2) non-adherence (<4 hours per night and clinical decision to withdraw therapy); (3) NIV no longer required; and (4) care transferred to another centre. Satisfactory adherence was defined as use >4 hours per day; however, NIV cessation was left to physicians' discretion.

Medical electronic record

Medical data were retrieved from the hospital electronic medical record by respiratory physicians using a standardised collection

sheet (MP, EL, AB) who checked and confirmed their accuracy. Collected data were gender, underlying respiratory disease and timing of NIV set-up. Timing of NIV set-up was defined as follows: elective admission for stable patients referred for respiratory review that were subsequently established on home NIV and following an acute episode for patients admitted for decompensated respiratory failure and for which, after clinical stabilisation but before hospital discharge, transfer to a specialist centre for home NIV set-up was decided to be clinically necessary. Data from technical databases were cross-checked with medical records and corrected accordingly. Based on the underlying pathology, patients were categorised into six different groups: neuromuscular disease (NMD), chest wall disease (CWD), obesity hypoventilation syndrome (OHS), obstructive sleep apnoea (OSA), obstructive airway diseases (OAD) or with an overlap between COPD and OSA (COPD-OSA overlap). For survival analysis, the NMD group was subdivided into rapidly progressive NMD (eg, motor neuron disease) or slowly progressive NMD (eg, Duchenne muscular dystrophy, myotonic dystrophy) (a full list of underlying neuromuscular disorders can be found in online supplementary eTable 1).

Statistical analysis

Continuous data are presented as mean and SD if normally distributed or median and IQR if non-normally distributed. Categorical data are presented as frequency counts and percentages. Comparisons were performed using Kruskal-Wallis test, χ^2 test, analysis of variance and Mann-Whitney test, as appropriate. Survival data were analysed using Kaplan-Meier method and log-rank tests. Patients for whom home NIV was withdrawn were censored at point of cessation of follow-up. Prognosis factors were analysed in univariate analysis and with a multivariate Cox model. For all tests, significance level was set at 0.05. Analyses were performed using SPSS V.23.0 and Prism V.6.0(h) for MacOs X (GraphPad Software, La Jolla, California, USA).

RESULTS

Diagnostic groups

Between 2008 and 2014, 1746 patients were established on home NIV, 1118 (64%) in London and 628 (36%) in Rouen (figure 1), with a median follow-up of 1.97 (0.78–3.78) years. Over the study period, the number of patients set up on home NIV increased by 5% per year, with 203 patients being set up in 2008 and 298 in 2014 (online supplementary eFigure 4). The baseline characteristics of the population are described in table 1. Patients set up in London were younger than patients set up in Rouen ($p=0.001$). The most frequent diagnostic category was OHS ($n=515$, 29.5%), followed by NMD ($n=397$, 22.7%), OAD ($n=334$, 19.1%) and COPD-OSA overlap ($n=221$, 12.7%). OSA and CWD were less frequent ($n=184$ (10.5%) and $n=95$ (5.4%), respectively). The distribution of diagnostic categories was different between the two centres ($p=0.007$). There were higher proportion of patients with NMD and lower proportion of patients with OAD in the London centre compared with Rouen ($p=0.001$).

Timing of NIV initiation and ventilator settings

Timing of NIV set-up (postacute and elective) and ventilator settings differed between centres. Patients with OAD were more likely to have their NIV set up following an acute admission (70%) than other groups of patients (NMD 42%, CWD 52%, OHS 49%, COPD-OSA 49% and OSA 22%; $p<0.001$).

The Rouen group had a higher proportion of NIV set-ups following an acute admission (60.5% vs 53.9%; $p<0.001$) and had a longer length of stay regardless of whether NIV was set up acutely or electively (elective admission for NIV set-up 2.0 days (2–4) ($p<0.001$) and non-elective admission 6.0 days (5–18) ($p<0.001$)). Ventilator device, mode, interface, pressure settings, backup rate and additional requirements varied between centres (table 2). The level of pressure support was significantly different over time ($p=0.0069$), with a higher pressure support in 2011 and 2012 when compared with 2008: 13.5 (11.0–17.0) and 14.0 (10.0–17.0) vs 13.0 (10.0–16.0) cmH₂O ($p=0.049$ and $p=0.002$, respectively). In each

Table 1 Baseline demographics of the study population

	Total population (N=1746)	London population (n=1118)	Rouen population (n=628)	P value
Age (years)	60.5 (±15.9)	58.8 (±15.7)	63.6 (±15.8)	<0.001
Gender (male), n (%)	949 (54)	613 (55)	336 (54)	0.617
PaCO ₂ at admission for NIV set-up (kPa)*	7.1 (6.2–8.1)	7 (6.1–8.0)	7.5 (6.6–8.8)	<0.001
Spirometry at NIV set-up†				
FEV ₁ (L)	1.1 (0.7–1.6)	1.1 (0.7–1.7)	1.0 (0.7–1.4)	0.078
FVC (L)	1.7 (1.2–2.4)	1.7 (1.1–2.4)	1.9 (1.4–2.4)	<0.001
Underlying respiratory disease				0.007
Neuromuscular diseases, n (%)	397 (22.7)	290 (25.9)	107 (17)	<0.001
Motor neuron disease	144 (36.3)	84 (29)	60 (56.1)	<0.001
Duchenne muscular dystrophy	49 (12.3)	37 (12.8)	12 (11.2)	
Postpolio syndrome	40 (10.1)	39 (13.4)	1 (0.9)	
Myotonic dystrophy	27 (6.8)	19 (6.6)	8 (7.5)	
Spinal cord injury	24 (6)	14 (4.8)	10 (9.3)	
Diaphragm palsy	21 (5.3)	13 (4.5)	8 (7.5)	
Other neuromuscular conditions‡	92 (23.2)	84 (29)	8 (7.5)	
Obstructive airway diseases, n (%)	334 (19.1)	199 (17.8)	135 (21.5)	0.001
COPD	305 (91.3)	182 (91.5)	123 (91.1)	0.733
Bronchiectasis	14 (4.2)	8 (4)	6 (4.4)	
Asthma	10 (3.0)	5 (2.5)	5 (3.7)	
Other obstructive conditions‡	5 (1.5)	4 (2)	1 (0.7)	
Chest wall diseases, n (%)	95 (5.4)	59 (5.3)	36 (5.7)	0.714
Kyphoscoliosis	58 (61.1)	32 (53.3)	26 (72.2)	0.003
Scoliosis	15 (15.8)	15 (25.0)	0 (0)	
Post-tuberculosis	10 (10.5)	3 (5.0)	7 (19.4)	
Pneumectomy	5 (5.3)	3 (5.0)	2 (5.6)	
Other restrictive conditions‡	7 (8.3)	7 (11.6)	1 (2.8)	
Obesity hypoventilation syndrome with or without obstructive sleep apnoea, n (%)	515 (29.5)	319 (28.5)	196 (31.2)	0.251
Obstructive sleep apnoea, n (%)	184 (10.5)	122 (10.9)	62 (9.9)	0.517
Overlap between obstructive airway disease and sleep apnoea, n (%)	221 (12.7)	129 (11.5)	92 (14.6)	0.072
COPD	206 (93.2)	122 (94.6)	84 (91.3)	0.588
Asthma	10 (4.5)	6 (4.7)	4 (4.3)	
Bronchiectasis	5 (2.3)	1 (0.8)	4 (4.3)	

Results are expressed in terms of mean and SD or median and IQR for continuous variable and in frequency for categorical values.

*n=1096.

†n=803.

‡Full list of other conditions can be found in online supplementary material.

COPD, Chronic obstructive pulmonary disease; NIV, non-invasive ventilation; PaCO₂, Partial pressure of carbon dioxide in arterial blood.

diagnostic group, ventilator settings used in the Rouen centre were lower than those used in London (figure 2). As part of the NIV set-up process supplementary oxygen was added to the ventilator circuit in 634 (36%) patients, with variation between diagnostic groups (OAD 64%, COPD-OSA overlap 49%, OHS 37%, CWD 33%, OSA 27% and NMD 10%; $p<0.0001$).

NIV adherence

NIV adherence to treatment was higher in Rouen than in London (7.6±4.6hours/day vs 5.5±3.6hours/day; $p<0.001$). NIV adherence varied according to the underlying diagnostic group (NMD 7.1 (4.0–9.5)hours/day; CWD 7.5 (4.1–9.3)hours/day; OAD 6.5 (3.7–8.7)hours/day; OHS 5.8 (3.0–7.8)hours/day; and OSA 5.5 (2.1–7.0)hours/day; $p<0.001$). NIV adherence was higher in all diagnostic categories in the Rouen group, with the exception of the NMD category (figure 2).

Survival

Following NIV initiation, overall survival was 6.63 years. Survival at 1 year, 3 years and 5 years was 85.9% (95% CI 83.2 to 86.6), 68.7% (95% CI 66.0 to 71.2) and 58.3% (95% CI 55.0 to 61.5), respectively, with a difference observed between the diagnostic categories ($p<0.001$). Survival was 1.0 (95% CI 0.7 to 1.2) year in the rapidly progressive NMD category, 6.3 years in the CWD category, 2.7 (95% CI 2.2 to 3.2) years in the OAD category, and 6.6 years in the COPD-OSA overlap category. Median survival was not reached in the slowly progressive NMD, OHS and OSA groups (figure 3). In an univariate analysis, the centre of NIV initiation did not have any impact on mortality ($p=0.358$), whereas age >60 years ($p<0.001$)

and having NIV set up following an episode of acute respiratory failure ($p<0.001$) were both associated with higher mortality. In a multivariate analysis, age, gender, timing of NIV set-up and underlying disease were significantly associated with survival (table 3). Analysis of the cohort with removal of rapidly progressive NMD did not impact on the variables associated with prognosis (online supplementary eTable 2).

DISCUSSION

These data represent the largest long-term outcome data of patients initiated on home NIV for treatment of chronic ventilatory failure. The overall 5-year survival following initiation of home NIV was poor at 58%; however, outcome varied according to the aetiology of respiratory failure, timing of NIV initiation, gender and age at initiation of home NIV. A clinical approach to improving NIV adherence and elective timing of initiation of home NIV may enhance outcome.

Survival outcome

The 1-year and 5-year survival of patients initiated on home NIV are 86% and 58%, respectively, which are worse than patients receiving therapy for idiopathic pulmonary fibrosis (1-year survival of 97%)²⁴ or pulmonary hypertension (5-year survival of 57%).¹³ As expected, survival varied depending on the underlying aetiology of chronic ventilatory failure. Patients with rapidly progressive NMD had a survival similar to previous published data.³ Patients with COPD had a similar survival to patients in the fourth quartile of the BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index,²⁵ and therefore

Table 2 Comparison of non-invasive ventilation set-up and setting between London and Rouen

	Total population (N=1746)	London population (n=1118)	Rouen population (n=628)	P value
NIV set-up following an acute respiratory failure (yes), n (%)	824 (48.6)	444 (53.9)	380 (60.5)	<0.001
Length of stay for NIV set-up following an acute respiratory failure	10 (5–18)	7 (3–17)	13 (9–18)	<0.001
Length of stay for NIV set-up following an elective admission	3 (2–4)	2 (2–3)	4 (3–4)	<0.001
Interface, n (%)				
Full face mask	1355 (77.6)	882 (78.9)	473 (75.3)	<0.001
Nasal mask	238 (13.6)	115 (10.3)	123 (19.6)	
pillows	64 (3.7)	33 (3)	31 (4.9)	
Nasal Total face mask	47 (2.7)	47 (4.2)	0 (0)	
Not available	42 (2.4)	41 (3.7)	1 (0.2)	
Life support NIV (yes)*, n (%)	609 (34.9)	515 (46.1)	94 (15)	<0.001
NIV mode, n (%)				
Pressure support	1405 (80.5)	859 (76.8)	546 (86.9)	<0.001
Pressure control	179 (10.3)	144 (12.9)	35 (5.6)	
Spontaneous	89 (5.1)	82 (7.3)	7 (1.1)	
Pressure support with target volume	40 (2.3)	11 (1)	29 (4.6)	
Not available	33 (1.9)	22 (2)	11 (1.8)	
Settings				
Positive inspiratory pressure (cmH ₂ O)	22±5	23±5	19±4	<0.001
Positive expiratory pressure (cmH ₂ O)	7±3	8±4	7±2	<0.001
Pressure support (cmH ₂ O)	14±5	15±5	12±3	<0.001
Backup rate (per minute)	13.2±2.5	13.4±2.8	12.8±1.6	<0.001
Additional oxygen (yes), n (%)	634 (36.3)	247 (22.1)	241 (38.4)	<0.001

Results are expressed in terms of mean and SD or median and IQR for continuous variable and in frequency for categorical values.

*Defined by a ventilator with built-in battery and approved for invasive ventilation.

NIV, non-invasive ventilation.

initiation of home NIV should trigger evaluation for lung transplantation or palliative care referral if lung transplantation is not appropriate.²⁶

Clinical implications

An important finding of the current study is the identification of two potentially modifiable factors associated with improved survival following initiation of home NIV. First, we have shown that NIV initiation following an episode of acute decompensated hypercapnic respiratory failure was associated with an increase in mortality. It can be postulated that patients presenting with decompensated respiratory failure would be further through the natural history of the disease and thus would be expected to have a higher mortality. Hence, early detection by screening may produce a lead time bias. However, data from patients with rapidly progressive NMD suggest that early initiation of NIV may improve the survival of these patients.^{27–28} An acute exacerbation of respiratory failure can cause further lung injury²⁹ and therefore lead to worse outcomes. Although we still lack early predictors of the onset of chronic respiratory failure, it can be speculated that close monitoring of patients at high risk of chronic hypercapnia would allow for earlier intervention and may therefore influence long-term outcomes. Similarly to most centres, such an approach was already established in our centres for patients with NMD with 3-monthly multidisciplinary follow-up. Such management could be extended to at-risk patients with OSA and COPD. However, there are no data with sufficient accuracy to provide reliable screening tools to predict early respiratory failure^{30–32} or evidence that such strategies are cost-effective.

Second, we have shown that an adherence to home NIV of greater than 4 hours per night was associated with an improved survival. To the best of our knowledge, our results are the first to show a correlation between adherence and mortality independent of the underlying disease. Interestingly, the cut-off of 4 hours of home NIV use per night was based on routine clinical practice, and studies in patients with eucapnic OSA treated with CPAP with this level of adherence leading to improvements in excessive daytime somnolence but not survival.^{33–35} Our results support the use of a 4 hours per night target for minimal adherence in all patients

with chronic ventilatory failure set up on home NIV, irrespective of underlying disease. However, in patients with advanced disease, adherence can be associated with a worse prognosis as increased use may reflect worsening respiratory failure. Interventions that can facilitate patient home NIV adherence, such as telemonitoring,³⁵ may have an impact on long-term outcome and should be the focus of future work. Better adjustments of ventilator settings may also contribute to improve adherence,³⁶ although such approach may need to be limited to a well-defined subgroup of patients,³⁷ as the use of polysomnography during NIV set-up remains controversial³⁸ and the lack of clear clinical efficacy is further impaired by practical constraints of delivering a high-cost low-availability intervention such as polysomnography.

Comparison with previous studies

Despite an increase in the total number of patients using home NIV², few data exist reporting long-term mortality. The only detailed data set previously reported was based on historical data and included patients on long-term oxygen therapy, and thus its relevance to the current population of home ventilation users is limited.¹⁴ Indeed, in this previous cohort the median survival of patients with 'chronic bronchitis' was 3 years. Interestingly, this reported survival is comparable with the current data in the OAD patient category, indicating little improvement in outcome in this patient group despite changes in pharmacotherapy and supportive care made over the last 20 years. Comparison with the study reported by Chailleux *et al*¹⁴ highlights the demographic change in home NIV. Chronic ventilatory failure, secondary to tuberculosis or poliomyelitis, is increasingly uncommon. The current data demonstrated that obesity-related respiratory failure (OSA and/or OHS) represents the most frequent indication for home NIV initiation.⁹ The use of CPAP may be considered as an alternative to NIV³⁹; however, in our cohort, the 3-year survival was slightly lower than that published by Masa and colleagues (82% vs 89%).⁴⁰ This could be explained by the fact that our population was unselected and that patients were frequently established after acute respiratory failure who were excluded in the Pickwick study. For patients with OAD, Köhnlein *et al*⁷ have reported a mortality rate of 10% at 1 year in patients established on home NIV. In our data, mortality rate for patients with OAD was 25% at 12 months. The

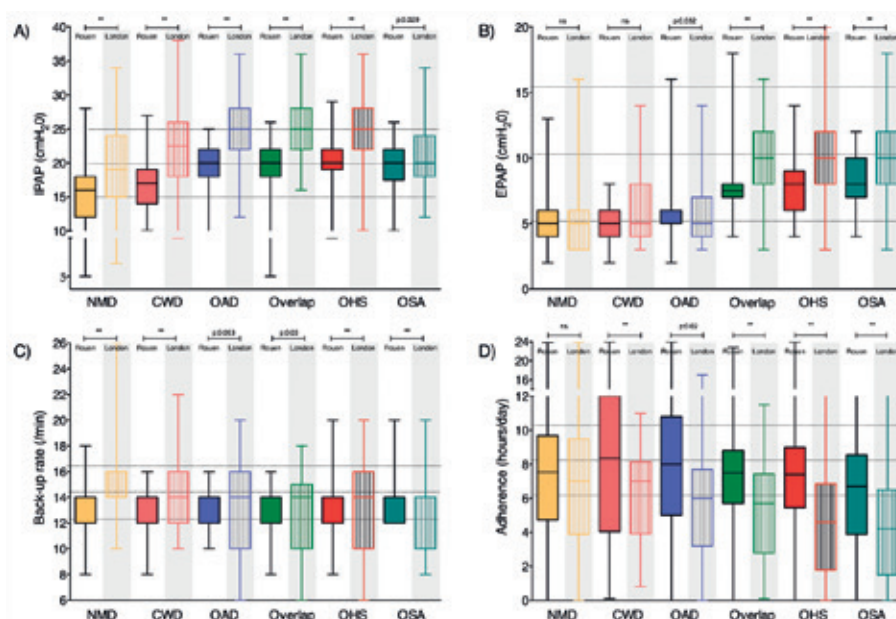


Figure 2 Comparison of NIV settings and adherence per day between London and Rouen according to diagnostic group. (A) Comparison of positive inspiratory pressure used. (B) Comparison of positive expiratory pressure used. (C) Comparison of backup rate used. (D) Comparison of adherence. Box with lines: London patients; coloured box: Rouen patients. Yellow: NMD; light red: CWD; blue: OAD; green: overlap; red: OHS; grey-green: OSA. ** $P < 0.001$; ns, not significant. CWD, chest wall disease; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, noninvasive ventilation; NMD, neuromuscular disease; OAD, obstructive airway disease; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnoea; overlap, overlap between OAD and OSA.

higher mortality seen in our data likely reflects that the patients recruited into the study by Köhnlein and colleagues⁷ required clinical stability, whereas clinical practice at the two centres was to initiate the majority of home NIV in OAD following an acute exacerbation, with a published mortality in this group in excess of 25% in recent clinical trials.^{6,41}

For patients with rapidly progressive NMD, we found a median survival rate of 1 year higher than that obtained in the initial randomised controlled trial in this group of patients.³ Similar to the other diagnostic groups the clinical population was more heterogeneous than the trial population. Our median survival is lower than that reported by Berlowitz *et al.*⁴² Again, this is likely to be explained by the significant proportion of patient set-ups occurring after an acute event in our data.

Increasing demand for home NIV

In the current study, the increase in NIV set-up was 5% per annum. This growth has been described in France¹⁰ and is explained by the increasing burden of obesity^{43,44} and obesity-related respiratory failure, with this diagnostic category now representing the most common indication for home NIV set-up. Changes in home NIV set-up for COPD may have been influenced by the results of two recent randomised clinical trials demonstrating the benefit of home NIV both in the chronic stable and postacute state.^{6,7} These data have been included in both national and international guidance,^{45–47} and it is expected that this would increase the referrals for home NIV in this patient group.

COPD-OSA overlap

Patients with COPD-OSA overlap syndrome have been shown to have significantly worse outcomes than patients with COPD alone.⁴⁸ However, these data are not confined to patients with respiratory failure. In the data reported here patients with respiratory failure caused by COPD-OSA overlap have an outcome that is between that of those patients with either obesity-related respiratory failure or COPD alone. The provision of positive airway pressure therapy has been shown to improve outcomes in patients with COPD-OSA, although the benefit on mortality may be confined to patients with hypercapnia.^{48,49} These data support the screening of patients with COPD-OSA overlap for the presence of hypercapnia to allow consideration of initiation or transition to NIV and provide an insight for future clinical trials comparing NIV with CPAP in this patient population.

Difference between the home NIV centres

This study compared two specialist home NIV centres, with different models of NIV management and integration with local healthcare organisations, although both university hospitals in urban areas. The data demonstrate variation in clinical practice between centres. Indeed, in Rouen, more patients were set up following an acute event. This can be explained by the fact that the London centre is a tertiary referral centre, whereas Rouen is a secondary care hospital. The London centre established significantly more patients on NIV in the study period as it covers a larger geographical area with more inhabitants than Rouen. Ventilator settings also varied between the centres, with the London centre using higher average ventilator pressures than the Rouen. However, the level of pressure per se is not a marker of efficacy. Indeed, patients in London were significantly younger suggesting a more severe disease and the proportion of overweight patients was higher in England than in France, which may impact on ventilatory requirement. In both centres, NIV was titrated in order to target significant CO₂ reduction measured with nocturnal transcutaneous CO₂ monitoring or evening-morning arterial blood gas. The similar long-term survival in both centres suggests adequate ventilator set-up despite the variation in pressures delivered. Further titration during follow-up may have minimised this difference. This difference in the level of pressure may explain why a higher proportion of full face masks were used in London. However, in the combined population the proportion of full face masks is similar to that previously reported.⁵⁰

Despite a higher home NIV adherence in Rouen, there was not an associated difference in mortality. This discrepancy may be explained by different factors. First, the lower pressures used to establish home NIV in Rouen may enhance comfort and tolerance; however, lessons learnt from COPD trials and in NMD⁵¹ emphasise the need for a control of respiratory failure to achieve clinical benefits. Second, a longer length of stay during set-up in Rouen may allow more time for training and education, improving adherence. Finally, the structure of the respective healthcare organisations⁵² may be responsible, with home follow-up by an external healthcare provider (ADIR Assistance) being used in Rouen, whereas London patients had hospital-based follow-up. Longer contact time and home visits may have facilitated greater patient understanding of the technique and treatment, promoting greater adherence. The organisation of home care delivery for respiratory

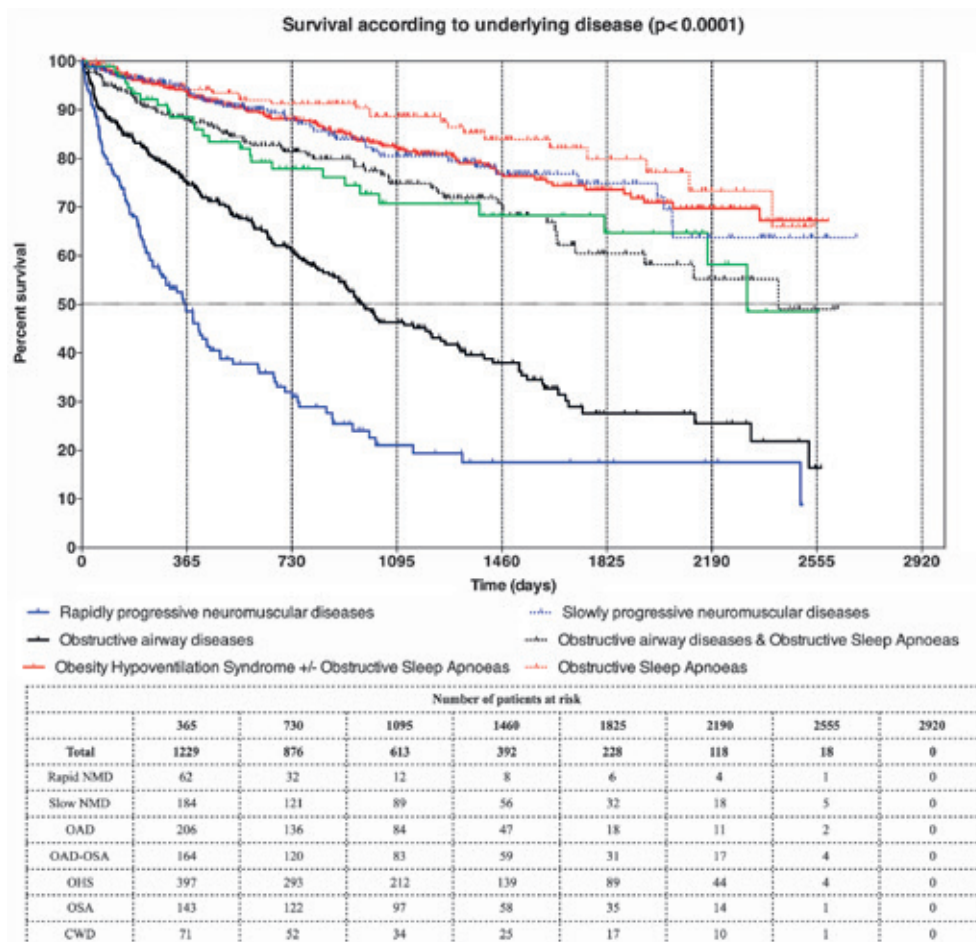


Figure 3 Survival curve after set-up of home non-invasive ventilation depending on underlying disease. Rapidly progressive neuromuscular disease group (rapid NMD: continuous blue), slowly progressive neuromuscular disease group (slow NMD: dashed blue), obstructive airway disease group (OAD: continuous black), overlap between COPD and OSA group (COPD-OSA: dashed black), chest wall disease group (CWD: light green), obesity hypoventilation syndrome group (OHS: continuous red) and obstructive sleep apnoea group (OSA: dashed red).

failure treatment in France relies on external care providers that have to comply with strict legal obligations. No study has demonstrated the costeffectiveness of this approach.

Limitations of the study

Inherent to the study design there are missing data and data that were not possible to validate in the medical record. However, we carefully chose the data to include variables that were prospectively

routinely collected in the clinical record to maximise integrity. This has led to one of the main limitations of the current study, which is the missing physiological data, in particular the baseline arterial blood gas measurement and spirometric data, as well as the arterial blood gas data after home NIV set-up. As these data were not always prospectively gathered, they were not included in the analysis for long-term outcome. Moreover, a significant proportion of patients were initiated on home NIV following an acute episode of

Table 3 Factors associated with mortality in univariate analysis (log-rank) and multivariate analysis (Cox regression)

	Univariate analysis (log-rank)		Multivariate analysis (Cox regression)	
	HR (95%CI)	P value	HR (95%CI)	P value
NIV centre (reference: Rouen)				
London	0.903 (0.756 to 1.079)	0.358	0.944 (0.778 to 1.145)	0.560
Gender (reference: male)				
Female	0.890 (0.749 to 1.058)	0.098	0.790 (0.652 to 0.959)	0.017
Age (reference: below 60 years old)				
Above 60 years old	3.131 (2.336 to 3.297)	<0.001	2.398 (1.912 to 3.008)	<0.001
Underlying respiratory disease (reference: overlap between obstructive airway disease and obstructive sleep apnoea)				
Rapidly progressive neuromuscular disease	4.349 (4.095 to 7.906)	<0.001	4.860 (3.432 to 6.881)	<0.001
Slowly progressive neuromuscular disease	0.655 (0.442 to 0.977)	0.038	0.852 (0.550 to 1.320)	0.474
Obstructive airway disease	2.475 (1.771 to 2.988)	<0.001	2.233 (1.623 to 3.073)	<0.001
Chest wall disease	1.016 (0.639 to 1.616)	0.0946	1.169 (0.723 to 1.891)	0.524
Obesity hypoventilation syndrome with or without obstructive sleep apnoea	0.633 (0.426 to 0.867)	0.006	0.721 (0.509 to 1.022)	0.066
Obstructive sleep apnoea	0.469 (0.318 to 0.748)	0.001	0.516 (0.315 to 0.844)	0.008
Timing of NIV set-up (reference: elective set-up)				
Set-up following an acute event	1.860 (1.545 to 2.203)	<0.001	1.376 (1.161 to 1.731)	0.001
Adherence (reference: below 4 hours per night)				
Adherence above 4 hours per night	1.110 (0.903 to 1.376)	0.315	0.636 (0.512 to 0.790)	<0.001

NIV, non-invasive ventilation.

decompensated acute on chronic ventilatory failure. As they were treated with acute NIV, no arterial blood gas value in the stable state was available. As we assessed adherence to NIV since NIV set-up, we were not able to analyse change in adherence over time that may be a better survival predictor especially in rapidly progressing disease. As we assessed adherence to NIV since NIV set-up, we were not able to analyse change in adherence over time that may signify end-stage disease in rapidly progressing disease. Finally, we did not collect changes in NIV settings during follow-up. These changes may reflect disease progression and may also act as a useful prognostic marker.

CONCLUSION

These data represent the largest long-term outcome data of patients initiated on home NIV for the treatment of chronic ventilatory failure. The 5-year survival following initiation of home NIV was almost 60%, with aetiology of respiratory failure, gender and age at initiation as key determinants of long-term survival. Potentially modifiable factors impacting on survival were NIV adherence and elective set-up of home NIV. Our results highlight the importance of organising dedicated pathways for patients with chronic respiratory failure in order to identify patients earlier and to provide adequate follow-up after NIV initiation in order to maximise adherence to treatment.

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Patient consent for publication Not required.

Ethics approval The study was approved by the local ethic committee of Rouen University Hospital, France (#E2017-21) and registered as a service evaluation at Guy's and St Thomas' NHS Trust, London, UK (#7511).

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REFERENCES

- Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 2005;25:1025–31.
- King AC. Long-Term home mechanical ventilation in the United States. *Respir Care* 2012;57:921–32.
- Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 2006;5:140–7.
- Pérez de Llano LA, Golpe R, Ortiz Piquer M, et al. Short-Term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity hypoventilation syndrome. *Chest* 2005;128:587–94.
- Borel J-C, Tamisier R, Gonzalez-Bermejo J, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. *Chest* 2012;141:692–702.
- Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017;317:2177–86.
- Köhnlein T, Windisch W, Köhler D, et al. Non-Invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014;2:698–705.

- Budweiser S, Hitzl AP, Jörres RA, et al. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. *Int J Clin Pract* 2007;61:1516–22.
- Janssens J-P, Derivaz S, Breitenstein E, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva lake area. *Chest* 2003;123:67–79.
- Melloni B, Mounier L, Laaban J-P, et al. Home-Based care evolution in chronic respiratory failure between 2001 and 2015 (Antadir Federation Observatory). *Respiration* 2018;96:446–54.
- King TE, Albera C, Bradford WZ, et al. All-Cause mortality rate in patients with idiopathic pulmonary fibrosis. Implications for the design and execution of clinical trials. *Am J Respir Crit Care Med* 2014;189:825–31.
- De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE–5—a population-based study. *Lancet Oncol* 2014;15:23–34.
- Benza RL, Miller DP, Barst RJ, et al. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the reveal registry. *Chest* 2012;142:448–56.
- Chailleux E, Fauroux B, Binet F, et al. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory. *Chest* 1996;109:741–9.
- Dreyer P, Lorenzen CK, Schou L, et al. Survival in ALS with home mechanical ventilation non-invasively and invasively: a 15-year cohort study in West Denmark. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:62–7.
- Budweiser S, Riedl SG, Jörres RA, et al. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. *J Intern Med* 2007;261:375–83.
- Kinnear W, Colt J, Watson L, et al. Long-Term non-invasive ventilation in muscular dystrophy. *Chron Respir Dis* 2017;14:33–6.
- Marti S, Pallero M, Ferrer J, et al. Predictors of mortality in chest wall disease treated with noninvasive home mechanical ventilation. *Respir Med* 2010;104:1843–9.
- Tan GP, McArdle N, Dhalwal SS, et al. Patterns of use, survival and prognostic factors in patients receiving home mechanical ventilation in Western Australia: a single centre historical cohort study. *Chron Respir Dis* 2018;15:356–64.
- Garner DJ, Berlowitz DJ, Douglas J, et al. Home mechanical ventilation in Australia and New Zealand. *Eur Respir J* 2013;41:39–45.
- Chailleux E, Fauroux B, Binet F, et al. Predictors of survival in patients receiving domiciliary oxygen therapy or mechanical ventilation. A 10-year analysis of ANTADIR Observatory. *Chest* 1996;109:741–9.
- Windisch W, Haenel M, Storre JH, et al. High-Intensity non-invasive positive pressure ventilation for stable hypercapnic COPD. *Int J Med Sci* 2009;6:72–6.
- Dreher M, Storre JH, Schmoor C, et al. High-Intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. *Thorax* 2010;65:303–8.
- Nathan SD, Albera C, Bradford WZ, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. *Lancet Respir Med* 2017;5:33–41.
- Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–12.
- Maddocks M, Lovell N, Booth S, et al. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *Lancet* 2017;390:988–1002.
- Sheers N, Berlowitz DJ, Rautela L, et al. Improved survival with an ambulatory model of non-invasive ventilation implementation in motor neuron disease. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:180–4.
- Lechtzin N, Scott Y, Busse AM, et al. Early use of non-invasive ventilation prolongs survival in subjects with ALS. *Amyotroph Lateral Scler* 2007;8:185–8.
- Donaldson GC, Seemungal TAR, Bhowmik A, et al. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847–52.
- Mokhlesi B, Masa JF, Brozek JL, et al. Evaluation and management of obesity hypoventilation syndrome. An official American thoracic society clinical practice guideline. *Am J Respir Crit Care Med* 2019;200:66–24.
- Mandal S, Suh ES, Boleat E, et al. A cohort study to identify simple clinical tests for chronic respiratory failure in obese patients with sleep-disordered breathing. *BMJ Open Respir Res* 2014;1:e000022.
- Borel J-C, Guerber F, Jullian-Desayes I, et al. Prevalence of obesity hypoventilation syndrome in ambulatory obese patients attending pathology laboratories. *Respirology* 2017;22:1190–8.
- Marin JM, Carrizo SJ, Vicente E, et al. Long-Term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–53.
- Barbé F, Durán-Cantolla J, Capote F, et al. Long-Term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 2010;181:718–26.
- Durán-Cantolla J, Aizpurua F, Montserrat JM, et al. Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial. *BMJ* 2010;341:c5991–1.
- Hannan LM, Rautela L, Berlowitz DJ, et al. Randomised controlled trial of polysomnographic titration of noninvasive ventilation. *Eur Respir J* 2019;53. doi:10.1183/13993003.02118-2018. [Epub ahead of print: 23 May 2019].
- Adler D, Perrig S, Takahashi H, et al. Polysomnography in stable COPD under non-invasive ventilation to reduce patient-ventilator asynchrony and morning breathlessness. *Sleep Breath* 2012;16:1081–90.
- Patout M, Arbane G, Cuvelier A, et al. Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial. *Thorax* 2019;74:83–6.
- Isak A, Ramsay M, Hart N, et al. BPAP is an effective second-line therapy for obese patients with OSA failing regular CPAP: A prospective observational cohort study. *Respirology* (Published Online First: 12 August 2019).
- Masa JF, Mokhlesi B, Benítez I, et al. Long-Term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. *Lancet* 2019;393:1721–32.
- Struik FM, Sprooten RTM, Kerstjens HAM, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014;69:826–34.
- Berlowitz DJ, Howard ME, Fiore JF, et al. Identifying who will benefit from noninvasive ventilation in amyotrophic lateral sclerosis/motor neurone disease in a clinical cohort. *J Neurol Neurosurg Psychiatry* 2016;87:280–6.
- Wang YC, McPherson K, Marsh T, et al. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet* 2011;378:815–25.
- GBD. Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2015;2017:13–27.
- Ergen B, Oczkowski S, Rochwerg B, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J* 2019;54:1901003.
- Windisch W, Geiseler J, Simon K, et al. German National Guideline for Treating Chronic Respiratory Failure with Invasive and Non-Invasive Ventilation: Revised Edition 2017 - Part 1. *Respiration* 2018;96:66–97.
- Windisch W, Geiseler J, Simon K, et al. German National Guideline for Treating Chronic Respiratory Failure with Invasive and Non-Invasive Ventilation - Revised Edition 2017: Part 2. *Respiration* 2018;96:171–203.
- Marin JM, Soriano JB, Carrizo SJ, et al. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnoea: the overlap syndrome. *Am J Respir Crit Care Med* 2010;182:325–31.
- Jaoude P, Kufel T, El-Solh AA. Survival benefit of CPAP favors hypercapnic patients with the overlap syndrome. *Lung* 2014;192:251–8.
- Callegari J, Magnet FS, Taubner S, et al. Interfaces and ventilator settings for longterm noninvasive ventilation in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2017;12:1883–9.
- Ogna A, Nardi J, Prigent H, et al. Prognostic value of initial assessment of residual hypoventilation using nocturnal Capnography in mechanically ventilated neuromuscular patients: a 5-year follow-up study. *Front Med* 2016;3:40.
- Stuart M, Weinrich M. Integrated health system for chronic disease management: lessons learned from France. *Chest* 2004;125:695–703.

Controle a asma^{1,2}

sem confundir os papéis.³



MAIOR CONTROLO
NUMA ÚNICA TOMA.^{1,2}



Revinty
furoato de fluticasona + vilanterol ELLIPTA
ELE CONTROLA

O perfil de segurança de Revinty foi validado em ensaios clínicos de grande escala, como o SUMMIT (n=4121) e SLS na Asma (n=2114)^{1,4}

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, 2019. Available at: <https://ginasthma.org/gina-reports/> (Acedido: março 2020). 4) Vestbo J et al. *Lancet* 2016;387:1817-1826. ICS: Corticosteroide inalado; LABA: Agonista β_2 de longa duração.

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). **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose **INDICAÇÕES TERAPÉUTICAS** Asma: Revinty Ellipta 92/22 mcg e 184/22 mcg está indicado para o tratamento regular da asma em adultos e adolescentes com idade ≥ 12 anos em que a utilização de um medicamento contendo uma associação (agonista beta2 de ação prolongada e corticosteroides para inalação) é adequada: doentes que não estão adequadamente controlados com corticosteroides para inalação e com agonistas beta2 de curta duração de ação conforme o necessário; doentes que estão já adequadamente controlados com corticosteroide para inalação e agonista beta2 de longa duração de ação. **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 média de corticosteroides para inalação em associação com um agonista beta2 de ação prolongada. Se os doentes não estiverem corretamente controlados com 92/22 mcg, a dose pode ser aumentada para 184/22 mcg. Os doentes devem ser regularmente reavaliados. A dose deve ser titulada para a dose mais baixa com a qual é mantido um controlo efetivo dos sintomas. Revinty Ellipta 184/22 mcg deve ser considerado para adultos e adolescentes ≥ 12 anos que requeiram uma dose mais elevada de corticosteroides para inalação em associação com um agonista beta2 de ação prolongada. Os doentes normalmente verificam uma melhoria na função pulmonar 15 minutos após a inalação. É necessário o uso diário regular para manter o controlo dos sintomas de asma e o uso deve ser continuado mesmo quando esta é assintomática. Se os sintomas surgirem no período entre as doses, deve ser tomado um agonista beta2 de curta duração, 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 é 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 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. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO** **Deterioração da doença** Não deve ser utilizado para tratar sintomas de asma aguda ou uma exacerbação aguda na DPOC, para os quais é necessário um broncodilatador de curta duração. O uso aumentado de broncodilatadores de curta duração para aliviar os sintomas indica deterioração do controlo. Os doentes não devem interromper a terapêutica na asma ou na DPOC, sem supervisão de um médico, uma vez que os sintomas podem reaparecer após a descontinuação. Os acontecimentos adversos e as exacerbações relacionadas com a asma podem ocorrer durante o tratamento. Deve pedir-se aos doentes que continuem o tratamento mas que procurem aconselhamento médico se os sintomas da asma continuarem incontroláveis ou piorarem após o início do tratamento com Revinty Ellipta. **Broncospasmo paradoxal** Pode ocorrer com um aumento imediato na pieira após a administração. Deve ser tratado imediatamente com um broncodilatador para inalação de curta duração. Revinty Ellipta deve ser suspenso imediatamente, o doente avaliado e uma terapêutica alternativa instituída conforme o necessário. **Efeitos cardiovasculares** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas por ex., taquicardia supraventricular e extra-sístoles. Num estudo controlado com placebo em indivíduos com DPOC moderada e com antecedentes, ou um risco aumentado de doença cardiovascular, não existiu aumento do risco de acontecimentos cardiovasculares. No entanto, deve ser utilizado com precaução em doentes com doença cardiovascular grave ou anomalias do ritmo cardíaco, tireotoxicose, hipocalcemia não corrigida ou em doentes com predisposição para níveis baixos de potássio sérico. **Doentes com compromisso hepático** Para os doentes com compromisso hepático moderado a grave, deve ser utilizada a dose de 92/22 mcg. **Efeitos sistémicos dos corticosteroides** Podem ocorrer com qualquer corticosteroide para inalação, em especial com doses elevadas receitadas durante longos períodos (ocorrência muito menos provável do que com corticosteroides orais). Incluem síndrome de Cushing, características cushingoides, apoplexia suprarrenal, diminuição na densidade mineral óssea, retardação do crescimento em crianças e adolescentes, cataratas e glaucoma e, mais raramente, uma variedade de efeitos psicológicos e comportamentais incluindo hiperatividade psicomotora, perturbações do sono, ansiedade, depressão ou agressão (em especial em crianças). Administrar com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. **Perturbações visuais** Podem ser notificadas perturbações visuais com o uso sistémico e tópico de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser considerado para encaminhamento para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, como coriorretinopatia serosa central (CRSC), que foram notificadas após o uso de corticosteroides sistémicos e tópicos. **Hiperlipcemia** Notificados casos de aumentos nos níveis de glucose no sangue em doentes diabéticos e tal deve ser considerado quando se receita a doentes com antecedentes de diabetes mellitus. **Pneumonia em doentes com DPOC** Um aumento da incidência de pneumonia, incluindo pneumonia que requer hospitalização, tem sido observado nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de um risco aumentado de pneumonia com o aumento da dose de esteroide mas isto não foi demonstrado de forma conclusiva entre todos os estudos. Não existe evidência clínica conclusiva para diferenças dentro da mesma classe na magnitude do risco de pneumonia entre os medicamentos contendo corticosteroides inalados. Os médicos devem continuar alerta para o possível desenvolvimento de pneumonia em doentes com DPOC pois as características clínicas de tais infeções sobrepõem-se aos sintomas das exacerbações da DPOC. Os fatores de risco para pneumonia em doentes com DPOC incluem tabagismo atual, idade avançada, índice de massa corporal (IMC) baixo e DPOC grave. **Pneumonia em doentes com asma** A incidência de pneumonia em doentes com asma foi frequente na dose mais elevada. A incidência de pneumonia em doentes com asma a tomar 184/22 mcg foi numericamente superior quando comparada com aqueles a receber 92/22 mcg ou placebo. Não foram identificados fatores de risco. **Excipientes** Cada dose administrada contém aproximadamente 25 mg de lactose (na forma mono-hidratada). Doentes com problemas hereditários raros de intolerância à galactose, deficiência total de lactase ou malabsorção de glucose-galactose não devem utilizar este medicamento. **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 infeções** Frequentes Pneumonia, infeção do trato respiratório superior, bronquite, gripe, candidase da boca e da garganta. **Doenças do sistema imunitário** Raras Reações de hipersensibilidade incluindo anafilaxia, angioedema, erupção cutânea e urticária. **Perturbações do foro psiquiátrico** Raras Ansiedade. **Doenças do sistema nervoso** Muito frequentes Cefaleia Raras Tremor. **Afeções oculares** Pouco frequentes Visão turva. **Doenças cardíacas** Pouco frequentes Extra-sístoles Raras Palpitações, taquicardia. **Doenças respiratórias, torácicas e do mediastino** Muito frequentes Nasofaringite Frequentes Dor orofaríngea, sinusite, faringite, rinite, tosse, disfonia Raras Broncospasmo paradoxal. **Doenças gastrointestinais** Frequentes Dor abdominal. **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia, dorsalgia, fraturas, espasmos musculares. **Perturbações gerais e alterações no local de administração** Frequentes Pirexia. **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda. **DATA DA REVISÃO DO TEXTO** dezembro 2018. **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 & Cª, S.A., -A Av. da Siderurgia Nacional, 4745-457, S.Mamede do Coronado; NIF: 500220913; DDVSA190129

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