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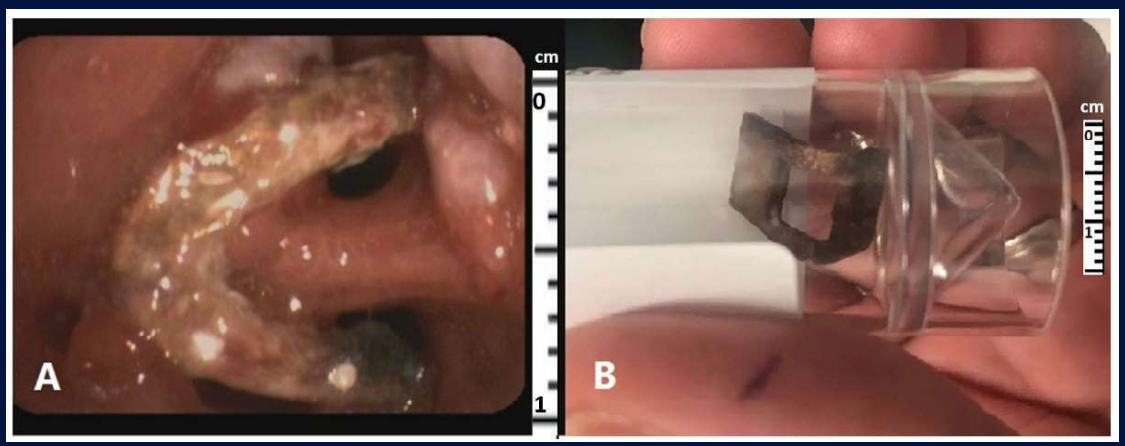

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Editorial

Estamos de regresso com mais um interessante número com artigos selecionados das revistas *Thorax* e *Archives of Disease in Childhood*.

Neste número da Revista, chamamos a sua atenção para alguns artigos.

O primeiro é o editorial "As intervenções integradas para deixar de fumar são essenciais para maximizar os benefícios de saúde do rastreio do cancro do pulmão". Os autores salientam o artigo original publicado no Thorax onde são apresentadas provas oportunas e muito necessárias sobre a forma ideal de intervenção para deixar de fumar no rastreio do cancro do pulmão.

O segundo artigo, "Poluição atmosférica e consultas respiratórias infantis em cuidados primários: uma revisão sistemática", teve como objetivo avaliar se as crianças num contexto de cuidados primários expostas a poluentes atmosféricos exteriores durante intervalos de curta duração correm um risco acrescido de diagnóstico respiratório. As evidências sugerem que o CO, SO_2, NO_2,PM_{10} e $PM_{2.5}$ são fatores de risco para doenças respiratórias em crianças.

No artigo seguinte, "Valor preditivo das medidas de função pulmonar para risco cardiovascular: um grande estudo de coorte prospetivo", os autores utilizaram modelos de risco para estimar as associações entre medidas de função pulmonar e resultados de doença cardiovascular (DCV), sendo que a capacidade preditiva foi determinada pelas análises da curva de decisão. Como conclusão, é possível ter em consideração os indicadores espirométricos na avaliação do risco de DCV, embora sejam necessários estudos de custo-eficácia e ensaios clínicos para pôr em prática a nova avaliação de risco de DCV.

No artigo "Concordância com as orientações para a realização atempada de imagiologia torácica após novas apresentações de dispneia ou hemoptise em cuidados primários: um estudo de coorte retrospetivo", foram analisados os dados interligados dos cuidados primários e dos exames imagiológicos hospitalares relativos a pacientes que apresentaram dispneia ou hemoptise durante um período de 5 anos. A principal conclusão do estudo foi que, apesar da probabilidade de realização de exames imagiológicos urgentes estar de acordo com o risco de diagnóstico de cancro subsequente, não foi requisitada imagiologia torácica urgente a uma grande percentagem de pessoas que apresentavam dispneia e hemoptise, o que indica oportunidades não aproveitadas para um diagnóstico mais precoce do cancro do pulmão.

Por último, salientamos uma estreia e uma novidade: um relevante artigo de opinião com o título "Novos indicadores da área respiratória nos cuidados de saúde primários – a evolução necessária" que descreve a recente atualização dos indicadores contratualizados nos cuidados de saúde primários para a área respiratória em Portugal referindo que as equipas de saúde passam agora a avaliar os cuidados de saúde a estes doentes com base em cinco indicadores de processo e gestão da doença (internamentos evitáveis por Asma, DPOC ou pneumonia). Este conjunto de indicadores tem uma influência de 14,2% no índice de desempenho da equipa, assumindo assim um papel de grande relevância.

Uma vez que a época de férias se aproxima, desejamos a todos que usufruam deste período para um excelente e merecido repouso e regressaremos em breve com novas escolhas.

Jaime Correia de Sousa

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Os eosinófilos no sangue assumem um papel central na previsão da resposta à imunoterapia sublingual (ITSL): uma toque familiar

Carlos Andrés Celis-Preciado,[1,2] Philippe Lachapelle,[1] Simon Couillard[1]

A imunoterapia sublingual (ITSL) representa uma imunoterapia com alergénios mais segura, mais confortável e mais conveniente do que a sua congénere subcutânea. Existe um número crescente de evidências que demonstram que a ITSL para ácaros do pó da casa (APC), erva, ambrósia e/ou pólen de árvores melhora os sintomas alérgicos e o controlo da asma.[1] Não é claro se a ITSL reduz consistentemente a ocorrência de ataques de asma.[1-3]

Publicado em 2016, o ensaio MITRA foi indiscutivelmente o ensaio controlado aleatorizado mais robusto que avaliou o efeito da ITSL (especificamente a APC-ITSL) na prevenção de ataques de asma na asma alérgica leve a moderada.[2] Resumidamente, o ensaio MITRA foi realizado em 834 pessoas com asma alérgica leve a moderada não controlada e imunoglobulina E (IgE) específica de alergénios APC positivos (≥0,7 kU/L ou >3 mm nos *cut-off* habituais de picada na pele). Após a aleatorização para APC-ITSL ou placebo, os participantes foram monitorizados com uma terapia estável de corticosteroides inalados (CEI) durante 7-12 meses, reduzindo depois a sua dose de CEI até à retirada completa nos 6 meses seguintes. Esta investigação patrocinada pela ALK-Abelló mostrou uma redução estatisticamente - e quase clinicamente significativa[4] - no risco de exacerbação moderada a grave nos braços de intervenção, independentemente da dose de APC-ITSL.

Na publicação original de MITRA,[2] apenas foram comunicadas algumas análises pré-especificadas de subgrupos "respondedores" na população do ensaio (idade, sexo, tipo de sensibilização a alergénios e co-sensibilização). Infelizmente, não foi identificado nenhum "grupo que respondedor a ITSL". A ausência de marcadores de diagnóstico deixou os médicos a selecionar aleatoriamente a quem propõem a ITSL, e as orientações sugerem suavemente que a APC-ITSL seja considerada como uma alternativa adicional para a asma alérgica leve a moderada não controlada.[3]

Um trabalho recente publicado na *Thorax*, Hoof *et al*, de um grupo de investigadores da empresa farmacêutica e de centros académicos, analisam mais de perto os fatores de previsão da resposta à APC-ITSL na população MITRA.[5] Especificamente, investigaram os valores preditivos de polimorfismos genéticos de nucleótido único (PNU), biomarcadores inflamatórios do tipo 2 (contagem de eosinófilos no sangue (CES), proteína catiónica eosinofílica sérica (PCE), triptase e testes de alergia (IgE total, títulos de IgE específicos para APC). Os autores analisaram se estes marcadores poderiam (1) prever o risco de ataques de asma no braço do placebo e (2) prever uma maior capacidade de resposta a APC-ITSL (ambos os braços de dosagem analisados em conjunto).

Os principais achados das análises *post-hoc* de Hoof *et al*[5] são os seguintes.

Primeiro, identificaram quais dos 22 PNU associados à asma estavam associados a uma modificação do risco de ataques de asma. Essencialmente, o genótipo T:T para o PNU rs7216389 no *locus* 17q12-21 foi o polimorfismo mais interessante para prever um risco de ataques de asma que poderia ser anulado com APC-ITSL. Esta observação foi replicada na coorte SARP3 - um passo de validação importante pelo qual elogiamos os autores.

Em segundo lugar, os investigadores avaliaram a relação entre os títulos de CES, PCE, triptase, IgE total e IgE específica com a probabilidade de ocorrência de um ataque de asma com placebo *versus* APC-ITSL. A Figura 2 do seu manuscrito original é autoexplicativa: CES, PCE e triptase previram ataques de asma no braço placebo que foram evitados nos braços APC-ITSL. É importante referir que os autores não demonstraram qualquer valor prognóstico ou teragnóstico para os títulos de IgE total e IgE específica para *Dermatophagoides pteronyssinus* e/ou *D. farinae* na população do ensaio MITRA (ver a figura suplementar S4 do artigo). A razão entre IgE específica e IgE total não foi avaliada.[6]

O terceiro resultado importante do artigo é a ausência de correlação entre os genótipos PNU e os endótipos tipo 2/alérgicos em pessoas com asma alérgica (figura suplementar S7).

Em conjunto, os principais resultados de Hoof *et al*[5] são novos e, na sua maioria, podem ter impacto na prática clínica. O facto de o PNU rs7216389 ter sido identificado e validado como um marcador genético do risco modificável (por APC-ITSL) de ataques de asma é novo e interessante. A ausência de correlação entre o genótipo, os biomarcadores inflamatórios do tipo 2 (CES, PCE, triptase) e os testes de alergia (IgE total, IgE específica) implica que a farmacogenómica é distinta do processo de fenotipagem clínica e de endotipagem inflamatória. Infelizmente, a genotipagem não está atualmente disponível nos cuidados clínicos normais, limitando assim a aplicabilidade clínica. Em contrapartida, o fenótipo inflamatório do tipo 2 é facilmente identificado na clínica. De facto, um hemograma completo com CES é um método amplamente acessível, barato e não invasivo para avaliar a atividade circulante das citocinas do tipo 2 (principalmente a interleucina (IL)-5). [7 8] No nosso centro, um hemograma completo é 15 vezes mais barato do que os testes de alergia, sendo que o primeiro apresenta resultados dias antes do segundo. É importante salientar que os especialistas em asma estão habituados a utilizar a CES para orientar a gestão terapêutica na asma grave[3 8], pelo que faz sentido incorporar este biomarcador na asma leve a moderada.

Como é que o achado de Hoof *et al* se enquadra no panorama atual da asma? Muito bem. Atualmente, na asma, são utilizadas várias estratégias avançadas de tratamento, desde a imunoterapia com alergénios (por exemplo, APC-ITSL) até aos anticorpos monoclonais (biológicos) que visam as citocinas do tipo 2 e as alarminas. Em todas estas estratégias orientadas, os biomarcadores da inflamação do tipo 2 demonstraram fortes valores de diagnóstico, mas não os testes de alergia (Quadro 1). Por conseguinte, a ausência de valor preditivo

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Quadro 1 Biomarcadores alérgicos e de tipo 2* com valor preditivo para a resposta a terapias orientadas na asma

Estratégia terapêutica	Biomarcador*	Valor preditivo para a resposta terapêutica	Referências
Anti-IgE (omalizumab)	CES	+	9 10
	FeNO	+	
	Testes de alergia	**0**	
Anti-IL-5/5R (mepolizumab, benralizumab, reslizumab)	CES	++	5
	FeNO	?	
	Testes de alergia	**0**	
Anti-IL-4R (dupilumab)	CES	+++	16-18
	FeNO	+	
	Testes de alergia	**0**	
Anti-TSLP (tezepelumab)	CES	+++	20
	FeNO	+++	
	Testes de alergia	**0**	

*Os biomarcadores indicados neste quadro são aqueles que são considerados clinicamente acessíveis (ou seja, não dependentes de laboratórios de investigação) no momento da redação (2023/2012).
Testes de alergia, sensibilização a alergénios aéreos testada com soro (IgE específica) ou picada na pele; CES, contagem de eosinófilos no sangue; FeNO, fração de óxido nítrico exalado; APC-ITSL, imunoterapia sublingual com ácaros do pó da casa; IgE, imunoglobulina E; IL, interleucina; R, recetor; TSLP, linfopoietina estromal tímica.

para a IgE total e a IgE específica no ensaio MITRA reflete as observações feitas com outra terapêutica antialérgica: o omalizumab, um anticorpo monoclonal de ligação à IgE. Em ensaios e coortes de mundo real com omalizumab, a CES e o óxido nítrico exalado fracionado (FeNO) foram marcadores preditivos de resposta, e não a IgE e a IgE específica.[9 10] Uma vez que o FeNO é um biomarcador distinto e complementar da inflamação do tipo 2 que avalia a atividade da IL-13 no compartimento das vias respiratórias,[8 11] é de perguntar qual terá sido a sua predição no risco de exacerbação da população de MITRA.

Devemos ter em mente duas advertências ao ler o artigo de Hoof *et al*. Em primeiro lugar, a análise é realizada numa população selecionada para ser sensibilizada a APC. Não foi determinado se a relação entre a IgE específica para APC e a resposta à ITSL é um "sim/não", por oposição a uma relação contínua. Em segundo lugar, apesar da ausência de valores prognósticos/preditivos dos títulos de IgE específica em MITRA, estes estão associados a piores sintomas de asma e a ataques de asma na asma de trovoada.[12] Isto pode dever-se ao facto de a IgE específica e a carga de alergénios preverem a gravidade das respostas alérgicas precoces, enquanto a resposta inflamatória do tipo 2 surge durante a resposta asmática tardia.[11]

Em conclusão, o estudo de Hoof *et al* é uma contribuição nova e impactante para os campos da respirologia e da alergia. Os autores demonstram que a eosinofilia sanguínea e a presença de um polimorfismo genético específico identificam asmáticos leves a moderados vulneráveis que podem beneficiar da APC-ITSL. A análise está muito de acordo com o paradigma do "traço tratável "[13] , que enfatiza a identificação das características do doente para orientar o tratamento. Esta é mais uma prova convincente a favor da gestão da doença das vias respiratórias, mesmo a leve a moderada, com base em marcadores de atividade patológica e de risco modificável,[14 15] em detrimento da dependência de predisposições e sintomas.[3]

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Incidência de tuberculose pós-pandemia: potencial sucesso da deteção ativa de casos?

Catherine M Stein

Até 2020, a tuberculose (TB) era todos os anos a doença infecciosa mais mortal a nível mundial. Quando a pandemia de COVID-19 teve início em 2020, a TB passou a ocupar o segundo lugar neste ranking, mas um segundo lugar muito próximo.[1] Os epidemiologistas da TB em todo o mundo ficaram muito preocupados com o que poderia acontecer com o fardo global da TB na sequência da pandemia, receando que o confinamento dos sistemas de saúde e as medidas de permanência em casa aumentassem a transmissão da TB, diminuíssem o acesso ao tratamento e ao rastreio e, em última análise, conduzissem a um aumento da incidência e da mortalidade.

Um trabalho recente de Kendall *et al*[2], publicado na revista Thorax, procurou responder a duas perguntas: qual foi o impacto da pandemia no Uganda e como é que os esforços de deteção ativa de casos de TB ajudaram? Neste estudo bem conduzido, foram realizadas campanhas de deteção ativa de casos (DAC) antes da pandemia em 2019 e após a pandemia em 2021. A proporção de casos de TB identificados através desta campanha desceu de 0,94% em 2019 para 0,54% em 2021. Os autores concluíram que a deteção ativa de casos de TB em toda a comunidade poderia ter um impacto significativo no fardo da TB a nível da população, mesmo na sequência da redução do acesso a instalações de diagnóstico e tratamento e do potencial aumento do contacto com indivíduos infecciosos no seio das famílias ou noutros círculos de contacto próximo. Estes achados, embora empolgantes, merecem consideração adicional tanto para os esforços da DAC como para o fardo da TB após a pandemia.

A DAC é valiosa na redução da transmissão da TB e, potencialmente, da mortalidade. A grande variedade de estratégias e benefícios é resumida numa revisão sistemática recente[3] e a importância da DAC como complemento da deteção passiva de casos é sublinhada noutra revisão recente.[4] Burke *et al*[3] concluíram que as evidências gerais sobre a eficácia da DAC eram mistas, embora esta pudesse reduzir a prevalência na comunidade se fosse aplicada com intensidade suficiente. Em alguns dos estudos resumidos nessa revisão, mas não em todos, as notificações de casos de TB diminuíram após campanhas intensivas de deteção de casos, o que é consistente com os achados de Kendall *et al*.[2]

Com a utilidade da DAC, também existem considerações importantes sobre a viabilidade, a logística, a implementação e a relação custo-eficácia. Uma análise recente da relação custo-eficácia concluiu que o êxito dos esforços da DAC depende de ferramentas de rastreio pouco dispendiosas, de baixa complexidade, sensíveis e altamente específicas.[5] Adicionalmente, os efeitos das intervenções da DAC também dependem da prevalência da TB, do ambiente construído, do acesso aos cuidados e das normas sociais.[3] Nem todos os estudos sobre a DAC revelam êxitos estrondosos. Estes estudos recentes salientam a importância de uma elevada cobertura destes esforços, de uma amostragem adequada de grupos marginalizados e outros grupos diversos, do desempenho do diagnóstico e das escolhas programáticas.[6 7] Algumas das razões potenciais para o sucesso dos esforços do estudo de Kendall *et al* são fatores como uma forte componente de mobilização comunitária e a presença regular de pessoal de investigação nas unidades de saúde locais. Estes fatores, que aumentaram a sensibilização, podem ser componentes valiosos para programas noutros contextos, embora, tal como referido por Garg *et al*, para que a DAC tenha impacto, a conceção destes esforços deve basear-se na compreensão do contexto.[6] Além disso, Coleman *et al*[4] defendem a integração do rastreio tanto da TB como da infeção latente por *Mycobacterium tuberculosis* (ILTB), embora a conhecida discordância entre o teste cutâneo da tuberculina e o ensaio de libertação de interferão-gama constitua um desafio.

Potencialmente mais controversa é a observação da redução da prevalência da TB pós-pandémica neste estudo, talvez sugerindo que o distanciamento social e outras restrições diminuem a incidência da TB em todos os contextos. Uma rápida amostragem da literatura recente sugere que esta não é uma conclusão universal. Estudos realizados no Canadá,[8] no condado de Hamilton em Ohio, EUA,[9] e no Brasil[10] revelaram uma diminuição das taxas de tratamento e rastreio da ILTB. Em geral, estes estudos concluíram que a diminuição do tratamento da ILTB não se deveu a uma diminuição da transmissão da TB. Por exemplo, no estudo em Ohio, os encaminhamentos aumentaram quando as restrições estaduais foram suspensas.[9] Se as taxas de ILTB forem constantes, existe a possibilidade de transmissão de TB caso a ILTB seja reativada. Um estudo no Uganda demonstrou um atraso na procura de cuidados para a TB sintomática[11] durante os períodos de confinamento, e outro observou que a prevalência de ILTB era idêntica durante os períodos de restrições e antes da pandemia.[12] Outra razão pela qual as notificações de TB podem ter diminuído foi o facto de o equipamento GeneXpert ter sido reutilizado para o diagnóstico da COVID-19 em alguns locais.[13] Todos estes estudos sugerem que a transmissão da TB continuou durante a pandemia. Por conseguinte, é provável que o impacto na epidemia global de TB devido aos procedimentos de controlo da COVID-19 tenha sido reduzido, mantendo-se a possibilidade de um aumento da incidência. Também é provável que o sucesso de Kendall *et al*[2] na redução da prevalência da TB se tenha devido à qualidade da sua campanha DAC específica, que deve ser elogiada. Mas é possível que estes benefícios se tenham verificado apenas nas áreas dessa campanha e não de forma generalizada.

Em conjunto, isto ilustra a necessidade de continuar a avaliar as intervenções da DAC, tanto enquanto abordagem de redução da prevalência da TB em geral, como também enquanto abordagem potencial durante eventos de saúde que desafiem o sistema de saúde existente. As reduções na prevalência da TB são provavelmente multicausais[2] e estas outras causas potenciais devem ser exploradas. Acresce que, tal como referido por Burke *et al*,[3] as futuras intervenções DAC requerem uma avaliação estatística formal. São necessários estudos adicionais e revisões sistemáticas para examinar de forma abrangente o impacto das restrições da COVID-19 na incidência da TB e na procura tardia de cuidados numa variedade de contextos, a fim de desenvolver melhores estratégias para o futuro. Estas análises primárias estão provavelmente em curso. As lições de estudos qualitativos de profissionais de saúde revelaram a importância de medidas alternativas de apoio aos doentes e de educação contínua,[13] o que é consistente com o potencial impacto positivo da DAC observado neste trabalho.[2] Para constatar o óbvio: se a DAC, as visitas domiciliárias e/ou a educação são abordagens eficazes contra a transmissão da TB, de onde virão os recursos humanos? Seja recorrendo à DAC ou a abordagens educativas acrescidas, é necessária uma sensibilização contínua sobre a TB para garantir que quaisquer perdas nos esforços de prevenção durante a pandemia de COVID-19 possam ser resolvidas. Os epidemiologistas da TB e os profissionais de saúde pública interessados em combater a TB em ambientes endémicos devem ler atentamente o trabalho de Kendall *et al*[2] para verem quais as lições que podem retirar.

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Identificar um subfenótipo hiperinflamatório da SDRA associado a piores resultados: a ferritina pode ajudar?

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A mortalidade atribuível à síndrome de dificuldade respiratória aguda (SDRA) é considerável. [1 2] No entanto, não foi demonstrado qualquer benefício em termos de sobrevivência em ensaios controlados e aleatorizados (RCT, do inglês *randomised controlled trials*) de estratégias farmacológicas para tratar a SDRA, o que se presume ser uma consequência da heterogeneidade dos processos clínicos e biológicos entre os doentes que cumprem os critérios para a SDRA.[3]

Numa tentativa de resolver a heterogeneidade, esforços recentes levaram à elucidação do papel do microbioma respiratório[4] e à identificação, tanto em doentes em risco de SDRA[5] como em doentes com SDRA[6], de subfenótipos reprodutíveis, tais como os subfenótipos "hipoinflamatório" e "hiperinflamatório", estando este último associado a piores resultados. Esses subfenótipos foram identificados através de análises *post hoc* de dados clínicos e de biomarcadores plasmáticos de doentes inscritos em ensaios clínicos aleatorizados ou em estudos observacionais.[5 6] A implementação de subfenótipos na prática clínica tem sido até agora limitada devido à falta de validação prospetiva, bem como à necessidade de medição rápida e em tempo real de múltiplos biomarcadores necessários para estratificar os doentes. Acresce que a medição desses biomarcadores só pode ser realizada em laboratórios de investigação. Por conseguinte, seria desejável que, em vez de múltiplos biomarcadores, se pudesse utilizar um único marcador rotineiramente disponível no contexto clínico para estratificar os doentes e, especificamente, identificar os doentes com SDRA em risco de piores resultados.

Numa edição recente da *Thorax*, Mehta *et al* avaliaram se a ferritina, um marcador rotineiramente disponível, poderia identificar doentes com SDRA em risco de mortalidade.[7] Os autores aproveitaram os dados individuais dos doentes de indivíduos previamente inscritos no estudo HARP-2 (a coorte de derivação; um RCT de sinvastatina *vs*. placebo) ou no estudo ROSE (a coorte de validação; um RCT de cisatracúrio contínuo com sedação profunda durante 48 horas *vs*. cuidados habituais sem bloqueio neuromuscular e com sedação mais leve). [8,9] Embora os critérios de inclusão fossem semelhantes, a relação entre a pressão parcial de oxigénio arterial e a fração de oxigénio inspirado para efeitos de inclusão era mais elevada em HARP-2 (<300 mm Hg) do que em ROSE (<150 mm Hg).[8 9] Em ambos os ensaios clínicos aleatorizados, o plasma foi recolhido nas primeiras 48 horas após o início da SDRA e antes da aleatorização. Os níveis de ferritina foram medidos em cada RCT recorrendo a *kits* ELISA disponíveis no mercado.[8 9] Utilizando um modelo de regressão logística com *splines* cúbicas restritas, os autores descobriram que um aumento equivalente a um *log* da ferritina estava associado a um OR de 1,71 para a mortalidade aos 28 dias.[7] Também determinaram que um limiar de ferritina >1380 ng/ml (presente em 28% dos doentes de HARP-2 e 24% dos doentes de ROSE) estava associado a uma maior mortalidade. Por fim, os autores realizaram uma análise de mediação demonstrando que a associação entre ferritina e mortalidade foi mediada pela interleucina (IL) 18 com um efeito pequeno, mas estatisticamente significativo, após o ajuste para confundidores, como a etiologia da SDRA e o *score* APACHE II. O raciocínio subjacente ao foco na IL-18 baseou-se em evidências anteriores que indicam que a ferritina promove a ativação do inflamassoma, que a IL-18 é um marcador substituto da atividade do inflamassoma e que os níveis de IL-18 estão elevados em doentes com SDRA.[10 11]

Existem vários pontos fortes no trabalho de Mehta *et al*.[7] Em primeiro lugar, os autores utilizaram dados e bioespécimes de dois ensaios clínicos aleatorizados.[8 9] A recolha de bioespécimes como prática de rotina em ensaios clínicos aleatorizados facilita muito o trabalho de investigação sobre subfenótipos da SDRA e a compreensão das trajetórias dos subfenótipos. Em segundo lugar, os autores selecionaram um marcador único e amplamente disponível na prática clínica (a saber, a ferritina) para identificar doentes com SDRA em risco de alta mortalidade. Níveis elevados de ferritina foram previamente associados à patologia hiperinflamatória e a maus resultados na linfohistiocitose hemofagocítica,[12] na sepses com características de síndrome de ativação semelhante à dos macrófagos (em que a hiperferritinemia foi utilizada para prever a resposta ao tratamento com anakinra)[13] e na COVID-19.[14] Embora o papel da hiperferritinemia nestes estados de doença não esteja totalmente esclarecido, as ligações anteriores entre níveis elevados de ferritina, ativação do inflamassoma e morte celular piroptótica fornecem uma premissa científica para avaliar a relação causal entre ferritina, IL-18 e mortalidade. O achado de Mehta *et al*[7] de que a IL-18 contribui como uma via intermediária entre a ferritina e a mortalidade pode justificar uma investigação mais aprofundada e específica da via da IL-18 em doentes hiperferritinémicos com SDRA.

Ao ler o elegante estudo de Mehta *et al*,[7] é preciso ter em mente duas considerações. Em primeiro lugar, a deteção de IL-18 no plasma pode não ser, por si só, necessariamente indicativa de ativação do inflamassoma e morte celular piroptótica. A IL-18 tem um grande número de funções estabelecidas, incluindo a indução de imunidade mediada por células durante a infeção.[15] Adicionalmente, ainda não é claro se o objetivo da IL-18 produziria um benefício clinicamente significativo, dada a mediação parcial (mas estatisticamente significativa) estimada nesta análise.[7] Em segundo lugar, existe atualmente uma falta de compreensão sobre como e se os níveis de ferritina se alteram durante o curso clínico. Os dados relativos às trajetórias dos subfenótipos na doença crítica são limitados até ao momento.[16] Um estudo alargou a análise de classes latentes em dois RCT de doentes com SDRA ao dia 3, onde dois subfenótipos foram novamente evidentes.[17] No entanto, não se sabe se a carga inflamatória e as implicações para a doença dos subfenótipos identificados na linha de base e ao dia 3 são os mesmos.[18] A utilização de dados de trajetória será de importância crítica em estudos futuros para obter uma compreensão mais profunda da cinética temporal de um subfenótipo específico, bem como para saber se os estados de doença podem ser modificados pelo tratamento. A resolução de um subfenótipo prejudicial, se estiver consistentemente associada a resultados a longo prazo centrados no doente, pode ser um parâmetro mais adequado para estudar do que a mortalidade.[18]

Em conclusão, Mehta *et al* são elogiados por seguirem uma abordagem pragmática para a subfenotipagem da SDRA com patologia hiperinflamatória, utilizando um único marcador prontamente disponível.[7] À medida que os esforços para identificar subfenótipos com utilidade clínica na SDRA continuam, é certo que surgirão mecanismos biológicos alternativos para os classificar, que podem ou não se sobrepor às descobertas anteriores. No entanto, esta abordagem de "tradução inversa", ou análise *post hoc* de bioespécimes de RCT que aproveita o poder da aleatorização, possui um potencial incrível para novas descobertas de subfenótipos.[19 20] Finalmente, a análise de mediação pode servir como uma abordagem estatística importante para identificar novos biomarcadores de base mecanicista para futuros objetivos terapêuticos e/ou monitorização da resposta ao tratamento.

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A função pulmonar como fator de previsão independente do risco de doença cardiovascular: implicações na prática clínica e na política

Tae Yoon Lee, Mohsen Sadatsafavi

A fisiologia intimamente interligada dos sistemas cardiovascular e pulmonar suscita vários fatores de risco e vias de doença partilhados, contribuindo significativamente para a elevada incidência de doenças cardíacas e pulmonares concomitantes.[1] Por exemplo, os indivíduos diagnosticados com asma possuem um risco 15%-53% mais elevado de doença cardiovascular (DCV),[2] enquanto os indivíduos diagnosticados com doença pulmonar obstrutiva crónica (DPOC) possuem um risco 2-5 vezes mais elevado de DCV.[3] A associação entre o comprometimento respiratório e a DCV não se restringe aos indivíduos com doenças respiratórias diagnosticadas. De facto, vários estudos demonstraram que o comprometimento da função pulmonar, independentemente do diagnóstico, está associado a um maior risco de DCV.[4 5]

No entanto, as implicações de tais associações para a prática clínica e para a elaboração de políticas têm se mantido pouco exploradas. A previsão de risco multivariável é a pedra angular da prevenção primária da DCV.[6] Por exemplo, a terapêutica com estatinas e as alterações de estilo de vida estão recomendadas para indivíduos sem antecedentes de DCV quando o seu risco previsto de DCV ao longo de 10 anos excede os 5%-10%.[7] A previsão de risco baseia-se nos fatores de risco tradicionais, incluindo a idade, antecedentes de tabagismo, a tensão arterial e os lípidos séricos. A relevância das medidas da função pulmonar na estimativa de risco de DCV depende do grau em que a função pulmonar se mantém como um fator de previsão de DCV, para além do risco previsto por uma ferramenta de pontuação.

Esta importante questão foi abordada no estudo de Zhou *et al*, publicado nesta edição da *Thorax* com artigos da *ADC*.[8] Comparativamente a estudos anteriores,[5 9] este estudo fornece informações únicas sobre o poder preditivo da função pulmonar adicionado ao risco de DCV previsto por ferramentas de pontuação de risco convencionais. Este estudo é bem conduzido em várias frentes. Em primeiro lugar, baseia-se numa amostra grande e amplamente fenotipada (UK Biobank, uma coorte aberta de participantes saudáveis com idades compreendidas entre os 37 e os 73 anos), fornecendo um número robusto de eventos de DCV (variando entre ~3000 e >20 000, dependendo da definição de DCV utilizada). Os autores estudaram os resultados compostos de DCV, tal como definidos por três algoritmos de classificação amplamente utilizados (algoritmo QRISK3, classificação do *American College of Cardiology/American Heart Association* e a ferramenta *SCORE*). Os resultados foram comunicados tanto estatisticamente, em termos de melhoria da estatística c e de reclassificação líquida, como em termos de utilidade clínica, medindo o benefício líquido através da análise da curva de decisão.[10]

Estes aspetos do desenho do estudo, em particular a análise do benefício líquido, fazem deste estudo um dos mais perspicazes até à data sobre a utilidade da função pulmonar na previsão do risco de DCV. As medidas de função pulmonar foram preditores independentes de DCV para os três algoritmos de classificação. Entre os vários índices de função pulmonar, o volume expiratório forçado em 1 segundo (FEV_1) surgiu como o mais consistentemente associado ao risco de DCV. As associações assumiram, de um modo geral, a forma de um "L": a função pulmonar comprometida foi associada a um risco acrescido de DCV, mas a associação diminuiu para valores normais e superiores aos normais. As associações foram mais fortes no caso de eventos de DCV fatais (risco associado a deficiências restritivas ou obstrutivas aumentado em >70%, em comparação com 20%-30% para todas as DCV). Esta situação suscita a questão de saber se, para além de estar associada a um risco acrescido de DCV, uma função pulmonar deficiente também está associada a uma maior mortalidade nos doentes que sofrem de eventos de DCV. É importante salientar que a função pulmonar demonstrou ser um fator de previsão de DCV, independentemente dos rótulos de diagnóstico de asma ou DPOC.

É necessário mencionar algumas limitações do estudo. Uma limitação importante é o facto de a população ser >95% branca. Este facto é particularmente relevante, uma vez que se sabe que a função pulmonar é altamente dependente da raça e da etnia.[11] Tal como reconhecido pelos autores, a coorte do estudo era mais saudável do que a população em geral. Não sabemos se as associações se mantêm após a inclusão de fatores como a presença de sintomas respiratórios. Este foi um estudo de modelação preditiva e, como tal, não fornece evidências sobre a modificabilidade do risco de DCV através de alterações na função pulmonar (discordamos respeitosamente da conclusão dos autores de que a modificação da função pulmonar pode ser apontada como um meio de redução do risco de DCV - pode ser esse o caso, mas o presente estudo não fornece tais evidências). Adicionalmente, os autores examinaram uma variável da função pulmonar de cada vez e, portanto, não elucidaram a capacidade preditiva combinada de várias medidas. Também notamos que a qualidade da espirometria em "mundo real" pode ser inferior à de um estudo clínico, o que potencialmente enfraquece as associações.

Em suma, estes achados fornecem uma imagem convincente de que a função pulmonar comprometida é um fator de risco independente para a DCV. No entanto, as consequências clínicas e políticas destes achados dependem da magnitude das associações. À primeira vista, os resultados numéricos parecem pequenos. Por exemplo, a melhoria da estatística c com a inclusão de medidas da função pulmonar situou-se entre 0,0003 e 0,0069. No entanto, sabe-se que a estatística c varia de acordo com pequenos valores, mascarando melhorias potencialmente grandes no poder preditivo real.[12] Os autores também relataram índices de reclassificação. Embora isso permita comparar a função pulmonar com outros fatores de risco de DCV, observamos que as métricas de reclassificação são conhecidas por exibirem propriedades estatísticas inaceitáveis e desaconselhamos a sua utilização em estudos futuros.[13]

Na nossa opinião, é a análise do benefício líquido que fornece os resultados mais interpretáveis e novos. Uma vez mais, os valores numéricos do benefício líquido da inclusão do FEV_1 como preditor de risco de DCV parecem baixos (0,007-0,033/100 indivíduos), mas isto depende do contexto. Considere um "Controlo de Saúde Cardíaca" de rotina utilizando QRISK3 para uma pessoa sem antecedentes de DCV. O benefício líquido da inclusão do FEV_1 no cálculo do risco pode ser interpretado em unidades de verdadeiro positivo ou falso positivo. Em unidades de verdadeiros positivos, equivale à identificação de mais três indivíduos que irão desenvolver DCV nos próximos 10 anos, em 10 000 indivíduos avaliados com QRISK3. Estes valores podem não justificar a inclusão obrigatória de métricas da função pulmonar nas ferramentas de classificação do risco de DCV, que são fortemente recomendadas para a prevenção primária da DCV. Os criadores de ferramentas de pontuação do risco de DCV devem, pelo contrário, dar prioridade ao ajuste das suas previsões em doentes com doenças pulmonares estabelecidas, especialmente a DPOC.[14]

Por outro lado, os cálculos do benefício líquido podem ser mais relevantes para as iniciativas de rastreio e deteção de casos de doenças respiratórias, cuja aceitação atual por parte dos decisores políticos e dos responsáveis pelo desenvolvimento de orientações não é tão forte como a da prevenção

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primária das DCV.[15 16] No rastreio e na deteção de casos com base na população, os pequenos benefícios acumulam-se rapidamente. Considere o cenário em que 20% da população do Reino Unido com idades compreendidas entre os 40 e os 64 anos subscreve um " Exame de Saúde Pulmonar" único através de espirometria. A utilidade clínica acrescida seria equivalente à identificação de mais 1060 indivíduos que irão desenvolver DCV nos próximos 10 anos, ou à prevenção de cerca de 10 000 indivíduos de serem incorretamente classificados como sendo de alto risco de DCV (e provavelmente mais ainda se esses programas se centrarem nos fumadores atuais ou nas pessoas com sintomas respiratórios). Dada a modificabilidade do risco de DCV, isto pode afetar a relação custo-eficácia deste tipo de programas. Assim, estes achados podem, e devem, informar o debate ativo sobre a utilidade do rastreio e da deteção de casos de doenças pulmonares.

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As intervenções integradas para deixar de fumar são essenciais para maximizar os benefícios de saúde do rastreio do cancro do pulmão

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Numa edição recente da revista *Thorax*, Williams *et al* apresentam provas oportunas e muito necessárias sobre a forma ideal de intervenção para deixar de fumar no rastreio do cancro do pulmão. Em 2022, o Comité Nacional de Rastreio do Reino Unido recomendou um rastreio objetivo do cancro do pulmão para os indivíduos identificados como sendo de alto risco e com idades compreendidas entre os 55 e os 74 anos. Este ano, o Governo do Reino Unido anunciou a implantação nacional de um programa de rastreio do cancro do pulmão com objetivos específicos e, no âmbito das suas recomendações, propôs a integração da prestação de serviços de cessação tabágica. A implementação de um programa deste tipo tem o potencial não só de melhorar os resultados do cancro do pulmão, mas também de prevenir ou reduzir o peso de várias doenças relacionadas com o tabagismo, incluindo as doenças cardiovasculares e respiratórias, bem como de vários cancros, através da implementação de um apoio à cessação tabágica. Os dados sugerem que a combinação do rastreio e da cessação tabágica diminui a mortalidade específica do cancro do pulmão e a mortalidade global.[1]

A evidência mostra que o rastreio do cancro do pulmão pode constituir um "momento de aprendizagem" para a cessação tabágica, um breve momento em que a motivação para deixar de fumar pode ser reforçada.[2 3] É provável que este cenário único aumente a perceção do risco de continuar a fumar, aumente a reação emocional ao tabagismo e desafie o autoconceito de fumador. Williams *et al* deram um importante contributo para a evidência da integração do apoio à cessação tabágica no rastreio do cancro do pulmão através dos resultados de dois ensaios, como o QuLIT 1 e o QuLIT 2. Os seus achados demonstraram que a oferta de apoio imediato à cessação tabágica, incluindo a prestação de farmacoterapia, no âmbito do programa de controlo da saúde pulmonar específico do Reino Unido, está associada a um aumento das taxas de cessação tabágica a longo prazo. O QuLIT 1 ofereceu uma consulta presencial inicial para deixar de fumar, ao passo que a pandemia de COVID-19 exigiu uma intervenção inteiramente baseada no telefone. Os dados combinados dos ensaios QuLIT1 e QuLIT2 indicaram taxas mais elevadas de abandono validadas de 12 meses e 7 dias no braço de intervenção em comparação com os cuidados habituais (12,1% vs. 4,7%; p<0,05). Curiosamente, os autores identificam que as taxas de abandono tabágico aos 12 meses foram mais elevadas na intervenção apenas por telefone (QuLIT2), mas salientam que é necessário ter cuidado na interpretação dos resultados, uma vez que os estudos não eram diretamente comparáveis. Estes achados vêm juntar-se à crescente base de evidências de que o apoio continuado e opcional à cessação tabágica, em detrimento de um aconselhamento muito breve e da sinalização para serviços baseados na comunidade, é a forma mais adequada de apoio para as pessoas com probabilidade de serem elegíveis para o rastreio do cancro do pulmão[4], mas salientam que a conceção ideal da intervenção é ainda desconhecida.

A integração do apoio à cessação tabágica baseado em evidências no âmbito do rastreio do cancro do pulmão seria uma utilização altamente eficaz de recursos de saúde limitados e tem o potencial de se traduzir em benefícios para a saúde no que respeita a uma série de doenças relacionadas com o tabagismo. No entanto, desafios como os cortes no orçamento da saúde pública para os serviços de cessação tabágica no Reino Unido terão um impacto provável na quantidade de serviços de cessação tabágica disponíveis e de profissionais de cessação tabágica com formação adequada que poderiam ser utilizados no âmbito do rastreio do cancro do pulmão.[5] Foram comunicadas disparidades na prestação de serviços, incluindo a falta de serviços comunitários de cessação tabágica para onde encaminhar os fumadores, nos locais existentes do *Targeted Lung Health Check* (controlo da saúde pulmonar) em Inglaterra e, nos locais onde existem serviços comunitários, os tempos de espera são longos.

O grau em que os programas de rastreio do cancro do pulmão aconselham os doentes sobre a cessação tabágica pode variar muito e os dados sobre a eficácia das intervenções específicas de cessação tabágica integradas nos ensaios de rastreio do cancro do pulmão são limitados. A determinação da abordagem ideal é, por isso, reconhecida como uma prioridade elevada por várias organizações de saúde.[6 7] O trabalho da colaboração para a cessação tabágica no exame pulmonar (SCALE) demonstrou que, para ajudar a maximizar o alcance das intervenções de cessação tabágica, é importante oferecer uma vasta gama de tratamentos de cessação.[8] Adicionalmente, as pessoas elegíveis para o rastreio do cancro do pulmão terão uma história de tabagismo de longa duração e terão provavelmente tentado deixar de fumar em vários momentos das suas vidas. Fora de um contexto de rastreio, uma população elegível para o rastreio do cancro do pulmão pode necessitar de uma forma de apoio comportamental mais intensiva e centrada na pessoa, devido às complexidades da mudança de comportamento para esta população.[9] Do mesmo modo, a necessidade de uma forma de intervenção mais intensiva (ou seja, apoio continuado de um profissional de cessação tabágica e fornecimento imediato de farmacoterapia) num contexto de rastreio do cancro do pulmão foi salientada numa revisão sistemática efetuada por Williams *et al*.[10]

Embora saibamos que as pessoas elegíveis para o rastreio pulmonar encaram positivamente a integração da cessação tabágica,[11 12] é necessária mais investigação centrada na participação que se centre na compreensão da forma de intervenção que melhor funciona para uma população elegível para o rastreio pulmonar. A investigação em curso para avaliar a exequibilidade e a eficácia das intervenções de cessação tabágica no rastreio por tomografia computorizada de baixa dosagem (TCBD)[13-15] irá esclarecer algumas questões ainda sem resposta nesta área. No entanto, a crescente base de dados demonstra claramente que investir na integração de uma intervenção de alta intensidade para deixar de fumar nos programas de rastreio do cancro do pulmão é uma componente vital de uma estratégia de saúde pública que terá um impacto positivo no cancro e nas doenças respiratórias e cardiovasculares. Não o fazer significa perder uma oportunidade sem precedentes de capitalizar a implementação generalizada do rastreio do cancro do pulmão no Reino Unido.

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Novos indicadores da área respiratória nos cuidados de saúde primários – a evolução necessária

A Asma e a DPOC são as doenças respiratórias crónicas mais prevalentes e estima-se que cerca de 10% da população sofra de alguma delas. No entanto, a maioria destas pessoas não tem a sua doença devidamente controlada, correndo risco de agravamento da função pulmonar, persistência de sintomas e agudizações, estas últimas representando eventos de inflamação aguda das vias aéreas, que nos casos graves são potencialmente fatais.[1-3]

A maioria destas pessoas não tem acompanhamento médico adequado, e em 2023, em Portugal, aproximadamente apenas 1/3 destes doentes tiveram uma consulta com o seu médico de família orientada especificamente para a doença. A falta de acompanhamento médico resulta numa percentagem significativa de pessoas sem o tratamento adequado para o controlo da doença, aumentando assim o risco destes eventos adversos.[4-6]

Em 2024, fruto da nova reforma dos cuidados se saúde primários, foi generalizado o modelo B das unidades de saúde familiar, com um sistema de pagamento remuneratório de incentivos financeiros baseados no desempenho. Este é avaliado num conjunto de 43 indicadores, nas diversas atividades clínicas e preventivas, e que compõem o índice de desempenho da equipa (IDE), uma métrica padronizada em escala de 0 a 100%. Com isto procedeu-se a uma grande atualização dos indicadores contratualizados na área respiratória (tabela). As equipas de saúde passam agora a avaliar os cuidados de saúde a estes doentes com base em cinco indicadores de processo e gestão da doença (consulta anual ao doente com Asma ou DPOC, qualificação do diagnóstico adequado, realização de espirometria, vacinação antigripal) e um novo indicador de integração de cuidados com impacto em saúde (internamentos evitáveis por Asma, DPOC ou pneumonia). No total, este conjunto de indicadores tem uma influência de 14,2% no IDE, assumindo assim um papel de grande relevância. [6,7]

Com esta importante reforma, procura-se incentivar as equipas de saúde a implementar consultas estruturadas de gestão da doença respiratória, com especial enfoque no controlo da Asma ou DPOC e na prevenção de agudizações, pneumonias e consequentes internamentos. Esta consulta deve ser realizada, preferencialmente, em equipa (médico e enfermeiro), com o enfermeiro de saúde a assumir um papel fundamental, que pode ir desde a avaliação da adesão e correta técnica inalatória até à avaliação de sintomas, com aplicação de questionários validados (ex. CARAT e CAT), e promoção da vacinação (antigripal, antipneumocócica, entre outras já existentes…). A abordagem pode incluir a combinação de acompanhamento não presencial e remoto dos utentes e agendamento oportuno e planeado de consulta presencial, bem como estratégias possíveis para melhorar a sua adesão e satisfação. [8,9]

A pessoa com Asma ou DPOC é habitualmente portadora de inúmeras comorbilidades, particularmente de natureza cardiovascular e endócrino-metabólica (como hipertensão, insuficiência cardíaca, diabetes, refluxo gastroesofácigico, rinosinusite alérgica, ansiedade ou depressão, etc…). Há, por isso, oportunidades nestas consultas de vigilância para abordar de forma integrada estas patologias, sendo que o controlo de uma se reflete inevitavelmente na outra, e o médico de família assume um papel fundamental como especialista habilitado para gerir a multimorbilidade. [10,11]

Com a implementação sistemática e rotineira da consulta anual (ou em alguns casos mais frequentemente) para a Asma e DPOC, espera-se que que o controlo destas patologias melhore à escala epidemiológica. Para tal, é crucial investir na literacia e capacitação dos utentes, por forma a que possam entender o alcance da adesão à terapêutica de controlo, da monitorização clínica regular, da identificação precoce de sintomas de agravamento ou agudização, da necessidade de prevenção (vacinal ou de exposição ambiental) e da capacidade de autogestão da doença. [12,13]

2024 é assim o ano de mudança na área respiratória, com a evolução necessária para que a Asma e a DPOC passem a estar na agenda do dia e para melhorar a saúde de cerca de um milhão de pessoas em Portugal.

Indicadores contratualizados em 2024 na área respiratória	Min. Aceitável	Min. Esperado	Max. Esperado	Máx. Aceitável	IDE*
2013.049.01 FL Proporção utentes c/ DPOC, c/ FeV1 em 3 anos	30	60	100	100	Sim 1.5%
2017.380.01 FL Prop. adultos c/ asma/DPOC/ bronq. cr., com diagn.	74	81	100	100	Sim 1.5%
2021.436.01 FL Proporção DPOC >= 40A, c/ cons. vigil. DPOC 1A	35	70	100	100	Sim 1.5%
2021.437.01 FL Proporção asma >= 18A, c/ cons. vigil. asma 1A	35	49	100	100	Sim 1.5%
2020.435.01 FL Proporção utentes com vacina gripe gratuita SNS	62	6	100	100	Sim 1.2%
Indicadores contratualizados através do indicador composto: 365 - Taxa internamentos evitáveis popul. adulta (ajust.)					
2017.355.01 FL Taxa internamentos p/ asma adultos jovens (ajust.)	0.0	0.0	2.5	4.5	
2017.356.01 FL Taxa internamentos p/ asma/ DPOC em adultos (ajust.)	0.0	0.0	155	220	Sim 7%
2017.363.01 FL Taxa de internamentos por pneumonia adultos (ajust.)	0.0	0.0	250	350	

* indicadores contratualizados no cálculo do IDE (Índice de desempenho específico da equipa) e com impacto nos suplementos remuneratórios em % relativa.

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Artigo original

ARTIGO ORIGINAL

O papel da oximetria noturna na avaliação da gravidade da apneia obstrutiva do sono em crianças com desenvolvimento típico: um estudo multicêntrico

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RESUMO

Contexto e objetivos A poligrafia cardiorrespiratória (PCR) é a tecnologia predominante utilizada para diagnosticar a apneia obstrutiva do sono (AOS) em centros terciários no Reino Unido. A oximetria de pulso noturna (OPN) é, no entanto, mais barata e mais acessível. Este estudo avaliou a capacidade dos índices de OPN para prever a AOS em crianças com desenvolvimento típico (DT).

Métodos Os índices de registos simultâneos de OPN e PCR foram comparados em crianças com DT (com idades entre 1 e 16 anos) encaminhadas para avaliação da AOS em três centros terciários. A AOS foi definida como um índice de apneia-hipopneia obstrutiva (IAHO) ≥1 evento/hora. As curvas de características de funcionamento do recetor avaliaram a precisão do diagnóstico dos índices de OPN, incluindo ODI3 (Índice de dessaturação de oxigénio a 3%), ODI4 (Índice de dessaturação de oxigénio a 4%), índice delta 12 s e a saturação mínima de oxigénio. Foram geradas tabelas duas a duas para determinar as sensibilidades e especificidades dos valores de cut-off de números inteiros para a previsão de IAHO ≥1, 5 e 10 eventos/hora.

Resultados Foram analisados os registos de 322 crianças com DT, 197 do sexo masculino (61,2%), com uma mediana de idade de 4,9 anos (intervalo de 1,1-15,6). O IAHO foi de ≥1/hora em 144 (44,7%), ≥5/hora em 61 (18,9%) e ≥10/hora em 28 (8,7%) casos. ODI3 e ODI4 apresentaram a melhor precisão diagnóstica. ODI3 ≥7/hora e ODI4 ≥4/hora previram a AOS em crianças com DT com sensibilidades/especificidades de 57,6%/85,4% e 46,2%/91,6%, respetivamente. ODI3 ≥8/hora foi o melhor preditor de IAHO ≥5/hora (sensibilidade 82,0%, especificidade 84,3%).

Conclusão O aumento de ODI3 e de ODI4 predizem a AOS em crianças com DT com elevada especificidade mas uma sensibilidade variável. A OPN pode ser uma alternativa para o diagnóstico de AOS moderada-grave quando o acesso à PCR é limitado. As baixas sensibilidades para detetar AOS ligeira significam que a PCR de confirmação é necessária se a OPN for normal.

Key messages

What is the key question?

▶ There is limited evidence regarding the ability of nocturnal pulse oximetry (NPO) to diagnose OSA in typically developing (TD) children.

What is the bottom line?

▶ This multi-centre study has evaluated the ability of a range of NPO indices to predict OSA in over 300 TD children.

Why read on?

▶ NPO may be a suitable alternative to PSG/CRP for diagnosing moderate-severe OSA but confirmatory PSG/CRP is needed if NPO is normal.

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INTRODUCTION

Obstructive sleep apnoea (OSA) is the most common form of sleep disordered breathing (SDB) in typically developing (TD) children, affecting 1–3%.[1] It causes numerous problems including cognitive impairment and behavioural difficulties.[1] Overnight polysomnography (PSG), which determines sleep stages using electroencephalogram, is considered the gold-standard test for diagnosing OSA.[2 3] Cardiorespiratory polygraphy (CRP), which estimates sleep time, is recognised as an acceptable alternative[2] with good diagnostic capability in populations with a modest to high pretest probability of OSA.[4] Use of PSG and CRP is limited to specialist centres due to their complexity and cost. Attention has therefore focused on nocturnal pulse oximetry (NPO), which can be undertaken at home or in hospital, is simpler to report and relatively inexpensive.[3 5 6]

The ability of NPO to detect OSA in children has been evaluated in multiple studies[7–14] with superior diagnostic accuracy (particularly specificity) for detecting moderate/severe OSA compared with mild OSA.[9 11–13] Sensitivity and specificity levels varied depending on the NPO parameters evaluated and cut-offs used; potentially because some studies included children with comorbidities. These children experience more challenging, multifactorial SDB with obstructive and non-obstructive components, which NPO cannot differentiate.[3] The heterogeneity of the population in previous studies means the results may not be applicable to specific groups of children in clinical practice. It remains unclear which NPO indices best predict OSA compared with CRP and PSG. Previous studies have used receiver operating characteristic (ROC) curves to report indices with optimum combined sensitivity and specificity.[12 14] There is, however, a need to understand the sensitivities and specificities of NPO indices to predict OSA over a range of cut-off values. Furthermore, not all previous studies used motion-resistant oximeters with shorter averaging times,[15] which provide improved diagnostic accuracy.[16]

This study aimed to report sensitivities and specificities of commonly used NPO indices over a range of values to determine the optimum cut-off values for predicting OSA in TD children.

METHODS

Study design

This study retrospectively compared simultaneous CRP and NPO recordings of consecutive children at three UK centres between May 2016 and May 2021 inclusive. Centres included University Hospital Southampton NHS Foundation Trust, Great Ormond Street Hospital for Children, London, and the Royal Hospital for Children Glasgow, which provide tertiary sleep services. Studies (undertaken at home or in hospital) were included for TD children aged 1–16 years referred to evaluate OSA. Children with comorbidities including obesity (body mass index SD score >3), haemoglobin disorders and those on oxygen therapy or non-invasive ventilation were excluded. Studies were excluded if less than 4 hours of artefact-free data (from either NPO or CRP) were obtained.

Data collection

CRP was recorded using SOMNOscreen (SOMNOmedics, Germany) (Southampton and Glasgow), SOMNOtouch (SOMNOmedics, Germany) (Southampton) or Embla (Natus, USA) (London). Respiratory effort was measured using thorax and abdominal respiratory inductance bands (RIP), alongside the derived RIP sum channel for surrogate marker analysis if required. Oxygen saturation (SpO_2) and pulse rate were measured by Nonin integrated probe. ECG, body position, movement and nasal pressure flow were routinely recorded, while video, audio and transcutaneous carbon dioxide were recorded in some children. All children underwent simultaneous standalone NPO (Masimo, USA) or oxicapnography via transcutaneous monitoring (TCM4 and TCM5; radiometer with inbuilt Masimo oximetry) with a 2-second averaging time.

CRP recordings were scored by sleep physiologists according to American Academy of Sleep Medicine (AASM) rules.[17 18] Each 30-second epoch was classified as 'estimated sleep' or 'wake'. Oxygen desaturations ≥3% were autoscored and then reviewed manually. Apnoeas were scored if there was ≥90% flow reduction from baseline for ≥2 breaths. They were classified as 'obstructive' if respiratory effort continued during absent flow, 'mixed' if part of the event had continued and part had cessation of respiratory effort, and 'central' if there was cessation of respiratory effort with an associated ≥3% desaturation or if the central apnoea lasted ≥20 s. Hypopnoeas were scored if there was ≥30% reduction in baseline flow for ≥2 breaths with an associated ≥3% desaturation. The RIP sum was used as a surrogate for nasal pressure flow if the flow sensor was removed by the child. Physiologists were not blinded.

Outcomes

The following NPO parameters were recorded: mean baseline SpO_2 (%), 3% Oxygen Desaturation Index (ODI3), 4% Oxygen Desaturation Index (ODI4), minimum SpO_2 (%), delta 12 s index as a measure of variability over 12 s (D12) and percentage of analysis time with SpO_2<94%, 92% and 90%. Visi-Download software (Stowood Scientific, UK) was used for analysis. This reports the above variables including whole number desaturations ≥3% or 4% from baseline/hour, that is, ODI3 refers to desaturations ≥4.0% and ODI4 refers to desaturations ≥5.0%. Visi-Download software uses artefact rejection software to identify oximetry trace sections of probe disconnection and low-signal confidence. These and probable wake sections (from diary cards or live monitoring of studies) were removed.

CRP data were downloaded using Domino software (Somnomedics) and Remlogic software (Embla). In this analysis, the mixed/obstructive apnoea–hypopnoea index (OAHI) (events/hour) was the outcome of interest.

Definitions

OSA was defined as OAHI ≥1/hour, moderate OSA as OAHI ≥5/hour and severe OSA as OAHI ≥10/hour.[3]

Statistical analysis

Data were stored in Microsoft Excel and analysed using SPSS (V.28). Normally distributed variables were summarised by mean and standard deviation (SD). Non-normally distributed variables were summarised by median and 5th–95th centiles. Groups were compared using the independent samples t-test (normally distributed data) or the Mann-Whitney U test (non-normally distributed data).

ROC curves were used to assess the diagnostic accuracy of ODI3, ODI4, D12, minimum SpO_2 and % time with SpO_2<94%, 92% and 90% to predict OAHI ≥1, 5 and 10/hour. An area under the curve (AUC) of 0.7–0.8 was considered acceptable, 0.8–0.9 as excellent and >0.9 as outstanding.[19] Two-by-two tables were generated to determine the sensitivity and specificity of whole number cut-off values of ODI3, ODI4 and minimum SpO_2. Positive and negative predictive values (PPV and NPV) were also calculated. For D12 and % time with SpO_2<94%, 92% and 90%, optimum cut-off values were derived from ROC curve coordinates. Further analysis was not undertaken for variables where AUC was less than 0.7. A sensitivity/specificity of 65–80% was considered 'moderate', a sensitivity/specificity of 80–90% as 'high' and a sensitivity/specificity of 90–100% as 'very high'.[1]

RESULTS

Participants

322 children were included; 197 (61.2%) were male. The median age of participants was 4.9 years (range 1.1–15.6). There were 144 children (44.7%) with OAHI ≥1/hour, 61 (18.9%) with OAHI ≥5/hour and 28 (8.7%) with OAHI ≥10/hour.

The mean baseline SpO_2 of participants with OSA was 97.2% and was similar across severities (table 1). Median ODI3 ranged from 4.13/hour in those without OSA to 8.08/hour in those with OAHI ≥1/hour and 19.72 in those with OAHI ≥10/hour. The median ODI4 was 1.83/hour in children without OSA compared with 3.67/hour in those with OSA (p<0.001). It was greatest in children with OAHI ≥10/hour at 10.27/hour. Mean D12 was 0.33 in children without OSA compared with 0.46 in those with OSA (p<0.001) and 0.67 in those with OAHI ≥10/hour (p<0.001).

ODI3 as a predictor of OSA

For ODI3, AUC ranged from 0.77 (95% CI 0.72 to 0.82, p<0.005) for predicting OAHI ≥1/hour to 0.90 (95% CI 0.83 to 0.98, p<0.005) for predicting OAHI ≥10/hour (figure 1). ODI3 ≥7/hour was associated with the best combination of sensitivity (57.6%) and specificity (85.4%) for predicting OAHI ≥1/hour. For OAHI ≥5/hour, ODI3 ≥8/hour provided high sensitivity (82.0%) and high specificity (84.3%) (table 2). The associated PPV and NPV were 54.9% and 95.2%, respectively (online supplemental table 1). For OAHI ≥10/hour, ODI3 ≥11/hour provided optimum combined sensitivity (85.7%) and specificity (85.4%) (table 2).

ODI4 as a predictor of OSA

For ODI4, AUC ranged from 0.76 (95% CI 0.71 to 0.82, p<0.005) for predicting OAHI ≥1/hour to 0.90 (95% CI 0.82 to 0.98, p<0.005) for predicting OAHI ≥10/hour (figure 2). ODI4 ≥2/hour provided the highest combined sensitivity and specificity for predicting OSA. However, when considering only ODI4 cut-offs with specificity >80%, ODI4 ≥4/hour provided the highest combined sensitivity (46.2%) and specificity (91.6%) for predicting OAHI ≥1/hour (table 2). For OAHI ≥5/hour, ODI4 ≥4/hour provided moderate sensitivity (75.4%) and high specificity (86.5%) with PPV and NPV of 56.8% and 93.8%, respectively (online supplemental table 1). For OAHI ≥10/hour, ODI4 ≥5/hour provided high sensitivity (85.7%) and specificity (85.7%) (table 2).

D12 as a predictor of OSA

The ability of D12 to predict OSA was moderate with AUC of 0.70 (95% CI 0.64 to 0.76, p<0.005). However, diagnostic accuracy was better for more severe OSA; AUC for OAHI ≥5/hour was 0.82 (95% CI 0.75 to 0.88, p<0.005) and for OAHI ≥10/hour, it was 0.85 (95% CI 0.75 to 0.94, p<0.005) (online supplemental figure 1).

D12 ≥0.44 provided the optimum combined sensitivity (51.0%) and specificity (85.4%) for predicting OAHI ≥1/hour (table 3). For OAHI ≥5/hour, D12 ≥0.44 was also associated with the highest combined sensitivity (73.8%) and specificity (79.2%). For OAHI ≥10/hour, D12 ≥0.50 provided optimum combined sensitivity and specificity with values of 78.6% and 87.4%, respectively.

Artigo original

Table 1 Summary of NPO results in study participants

	All children (n=322)	OAHI <1/hour (n=178)	OAHI ≥1/hour (n=144)	OAHI ≥5/hour (n=61)	OAHI ≥10/hour (n=28)
Mean baseline SpO_2 (%)*	97.2±5.51	97.0±7.35	97.3±1.19 (p=0.651)	97.0±1.26 (p=0.968)	96.9±1.47 (p=0.924)
Minimum SpO_2 (%)†	90.0 (78.2–95.0)	91.0 (82.0–95.0)	89.0 (73.5–95.0) (p<0.001)	85.0 (69.0–93.9) (p<0.001)	82.5 (49.8–95.2) (p<0.001)
ODI3 (events/hour)†	4.29 (0.84–22.85)	4.13 (0.80–11.52)	8.08 (1.24–31.38) (p<0.001)	13.30 (2.53–38.87) (p<0.001)	19.72 (2.43–50.37) (p<0.001)
ODI4 (events/hour)†	1.91 (0.29–11.73)	1.83 (0.23–5.29)	3.67 (0.36–18.88) (p<0.001)	7.00 (1.22–25.46) (p<0.001)	10.27 (0.78–34.83) (p<0.001)
Delta 12 s index*	0.39±0.20	0.33±0.12	0.46±0.25 (p<0.001)	0.58±1.50 (p<0.001)	0.67±0.38 (p<0.001)
% time with SpO_2 <94%†	0.11 (0.00–5.01)	0.08 (0.00–1.48)	0.25 (0.00–15.63) (p<0.001)	1.06 (0.00–19.19) (p<0.001)	1.87 (0.00–31.65) (p<0.001)
% time with SpO_2 <92%†	0.03 (0.00–1.28)	0.01 (0.00–0.26)	0.07 (0.00–3.66) (p<0.001)	0.37 (0.00–8.89) (p<0.001)	0.63 (0.00–12.22) (p<0.001)
% time with SpO_2 <90%†	0.00 (0.00–0.64)	0.00 (0.00–0.12)	0.02 (0.00–1.64) (p<0.001)	0.11 (0.00–3.19) (p<0.001)	0.29 (0.00–1.70) (p<0.001)

P values refer to comparison of each group with children without OSA (OAHI <1/hour).
*Data reported as mean±SD.
†Data reported as median (5th–95th centiles).
NPO, nocturnal pulse oximetry; OAHI, obstructive apnoea–hypopnoea index; ODI3, 3% Oxygen Desaturation Index; ODI4, 4% Oxygen Desaturation Index; SpO_2, oxygen saturation.

Minimum saturation (SpO_2) as a predictor of OSA

The diagnostic accuracy of minimum SpO_2 for identifying children with OAHI ≥1/hour was poor with AUC of 0.65 (95% CI 0.59 to 0.71, p<0.005). AUC was higher for OAHI ≥5/hour (0.76, 95% CI 0.69 to 0.83, p<0.005) and OAHI ≥10/hour (0.79, 95% CI 0.68 to 0.89, p<0.005) (online supplemental figure 2). The sensitivity and specificity values for minimum SpO_2 as a predictor of OAHI ≥5/hour and 10/hour are shown in online supplemental table 2.

Percentage of analysis time with saturation (SpO_2) <94%, 92% and 90%

The diagnostic accuracy of percentage of time with SpO_2<94%, 92% and 90% was poor for OAHI ≥1/hour with AUC values of 0.69, 0.69 and 0.66, respectively (online supplemental figures 3–5). Diagnostic accuracy was, however, good for severe OSA with AUC values of 0.84, 0.86 and 0.82, respectively (online supplemental figures 3–5). Online supplemental tables 3–5 show the optimum cut-off values for predicting OAHI ≥5 and 10/hour.

DISCUSSION

This study explored the ability of NPO indices to predict OSA in TD children with suspected OSA. Previous studies evaluating the diagnostic accuracy of NPO to predict OSA included children with and without comorbidities and focused primarily on optimum combined sensitivity/specificity. Based on area under the ROC curve, ODI3 and ODI4 had the best diagnostic accuracy. For all NPO indices, AUC was greater for more severe OSA. For minimum SpO_2 and % time with SpO_2 <94%, 92% and 90%, AUC was <0.7 for OAHI ≥1/hour, suggesting that these indices cannot accurately predict mild OSA.

ODI3 >7/hour and ODI4 >4/hour are the recommended cut-offs for abnormality in children over 2 years of age.[1 15 20] We found that ODI3 ≥7/hour and ODI4 ≥4/hour predicted OSA in children with high specificity (85.4% and 91.6%, respectively) but poor sensitivity (57.6% and 46.2%, respectively). However, our findings suggest that ODI3 ≥8/hour is a more appropriate intervention threshold than ODI3 ≥7/hour because ODI3 ≥8/hour was associated with superior specificity for OAHI ≥5/hour. For OAHI ≥10/hour, we recommend using cut-off values of ≥11/hour for ODI3 and ≥5/hour for ODI4. In keeping with our findings, previous studies evaluating the role of NPO in diagnosing OSA have also demonstrated superior diagnostic accuracy for severe compared with mild OSA.[9 11 12]

Optimum cut-off points may depend on the population studied. Van Eyck et al found that ODI3 >4.31/hour predicted OAHI >1/hour with sensitivity and specificity of 50% and 93%, respectively, in 130 obese children.[21] In our sample of non-obese TD children, specificity >90% was only achieved with ODI3 cut-offs of ≥8. In children with Down syndrome, Hill et al demonstrated that D12 >0.555 was the best NPO predictor of OAHI ≥5/hour (sensitivity 92%, specificity 65%).[14] We found, however, that a lower cut-off (D12 ≥0.44) was a better predictor of OAHI ≥5/hour (sensitivity 73.8%, specificity 79.2%). These differences highlight the importance of studying different patient groups and interpreting findings in clinical context. When interpreting PPV and NPV, disease prevalence is an important consideration. Low prevalences of moderate-severe OSA in our cohort may explain the low PPV for ODI3 and ODI4 for predicting OAHI ≥5/hour and OAHI ≥10/hour. However, high NPVs in our cohort mean that moderate-severe OSA can be ruled out in 95.2% and 93.8% of children with ODI3 <8/hour and ODI4 <4/hour. It is unsurprising that minimum SpO_2 and time with SpO_2<94%, 92% and 90% were less accurate predictors of OSA, as these probably relate to other physiological functions such as lung capacity and ventilation–perfusion matching.

Table 2 Sensitivity and specificity values for a range of whole number ODI3 and ODI4 cut-off values for predicting OAHI ≥1, 5 and 10/hour

	OAHI ≥1/hour		OAHI ≥5/hour		OAHI ≥10/hour	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
ODI3 ≥ (events/hour)						
5	65.3% (94/144)	75.3% (134/178)	86.9% (53/61)	67.4% (176/261)	96.4% (27/28)	62.2% (183/294)
6	61.1% (88/144)	81.5% (145/178)	83.6% (51/61)	73.2% (191/261)	89.3% (25/28)	67.3% (198/294)
7	**57.6% (83/144)**	**85.4% (152/178)**	83.6% (51/61)	77.8% (203/261)	89.3% (25/28)	71.4% (210/294)
8	51.4% (74/144)	90.4% (161/178)	**82.0% (50/61)**	**84.3% (220/261)**	89.3% (25/28)	77.6% (228/294)
9	46.5% (67/144)	92.1% 164/178)	77.0% (47/61)	87.0% (227/261)	89.3% (25/28)	81.0% (238/294)
10	42.4% (61/144)	93.8% (167/178)	68.9% (42/61)	88.5% (231/261)	85.7% (24/28)	83.7% (246/294)
11	40.3% (58/144)	94.9% (169/178)	65.6% (40/61)	89.7% (234/261)	**85.7% (24/28)**	**85.4% (251/294)**
12	31.9% (46/144)	93.5% (170/178)	52.5% (32/61)	91.6% (157/260)	71.4% (20/28)	88.4% (260/294)
13	27.8% (40/144)	96.1% (171/178)	50.8% (31/61)	93.9% (245/261)	71.4% (20/28)	90.8% (267/294)
ODI4 ≥ (events/hour)						
2	**72.0% (103/143)**	**69.1% (123/178)**	90.2% (55/61)	60.4% (157/260)	92.9% (26/28)	54.9% (161/293)
3	55.2% (79/143)	80.9% (144/178)	83.6% (51/61)	76.2% (198/260)	89.3% (25/28)	70.0% (205/293)
4	46.2% (66/143)	91.6% (163/178)	**75.4% (46/61)**	**86.5% (225/260)**	89.3% (24/28)	80.9% (237/293)
5	38.5% (55/143)	93.8% (167/178)	68.9% (42/61)	90.8% (236/260)	**85.7% (24/28)**	**85.7% (251/293)**
6	32.2% (46/143)	96.1% (171/178)	59.0% (36/61)	93.5% (243/260)	75.0% (21/28)	89.1% (261/293)
7	25.2% (36/143)	96.6% (172/178)	50.8% (31/61)	95.8% (249/260)	67.9% (19/28)	92.2% (270/293)

Values with the optimum combined sensitivity and specificity are highlighted in bold.
OAHI, obstructive apnoea–hypopnoea index; ODI3, 3% Oxygen Desaturation Index; ODI4, 4% Oxygen Desaturation Index.

Strengths and limitations

To our knowledge, this is the largest study to date to explore the role of NPO in diagnosing OSA in TD children. Clinicians can use the results to determine optimum cut-off points for diagnosing OSA or referring for further investigation dependent on their patient population. Use of simultaneous NPO and CRP recordings ensures results are directly comparable, without influence of night-to-night variability.

There are limitations to this study: first, selection bias; children with severe OSA who were diagnosed based on symptoms and NPO alone are not represented. Second, CRP rather than PSG was used to diagnose OSA. Therefore, sleep time was estimated and OAHIs may have been underestimated due to underscoring of hypopnoeas not associated with desaturations. If PSG had been used, the classification of different levels of OSA may have been different. All studies were, however, scored according to AASM guidelines[17 18] and use of CRP to diagnose OSA in children is an accepted approach.[2 22]

The findings of this study only apply to data obtained from Masimo or TCM Masimo oximeters and analysed using Visi-Download software. This is, however, one of the most used software packages for analysing NPO data so the study results are still widely applicable. Further work could be undertaken to determine whether any other parameters, for example, mean SpO_2 nadir are predictors of OSA or whether a score combining different parameters improves diagnostic accuracy. Furthermore, diagnostic accuracy

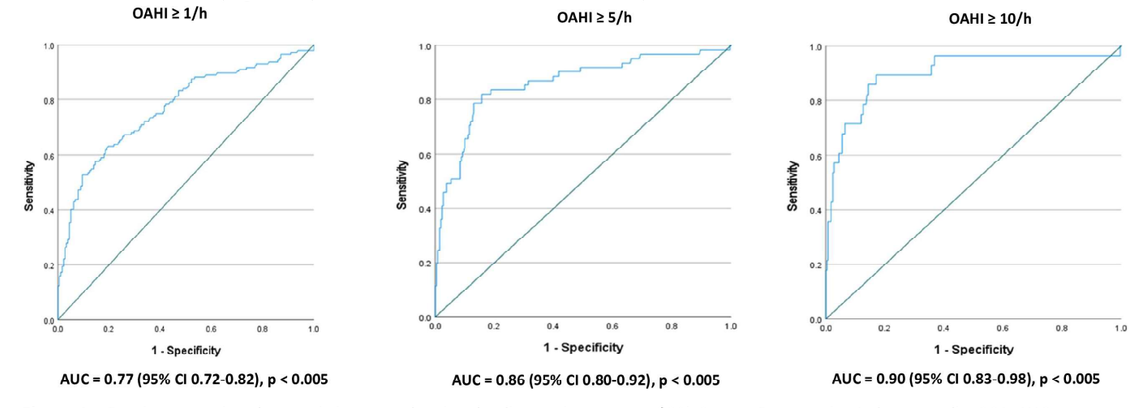

Figure 1 Receiver operating characteristic curves showing the diagnostic accuracy of 3% Oxygen Desaturation Index to predict OSA. AUC, area under the curve; OAHI, obstructive apnoea–hypopnoea index; ODI3, number of 3% oxygen desaturation; OSA, obstructive sleep apnoea.

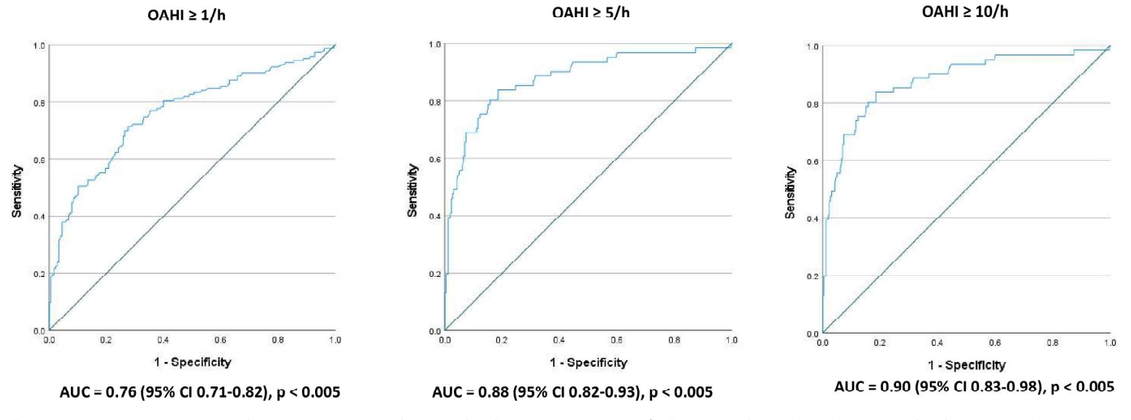

Figure 2 Receiver operating characteristic curves showing the diagnostic accuracy of ODI4 to predict OSA. AUC, area under the curve; OAHI, obstructive apnoea–hypopnoea index; ODI4, 4% Oxygen Desaturation Index; OSA, obstructive sleep apnoea.

Table 3 Sensitivity and specificity values for a range of delta 12 s (D12) index cut-off values for predicting OAHI ≥1, 5 and 10/hour

	OAHI ≥1/hour		OAHI ≥5/hour		OAHI ≥10/hour	
D12 ≥	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
0.37	66.4%	66.3%	83.6%	60.0%	89.3%	55.6%
0.38	62.9%	69.7%	80.3%	63.5%	89.3%	59.4%
0.39	60.8%	75.3%	78.7%	68.1%	85.7%	63.5%
0.40	58.0%	75.8%	77.0%	69.6%	85.7%	65.2%
0.41	55.9%	78.7%	77.0%	72.7%	85.7%	67.9%
0.42	54.5%	80.3%	77.0%	74.6%	85.7%	69.6%
0.43	51.7%	82.6%	75.4%	77.3%	85.7%	72.4%
0.44	**51.0%**	**85.4%**	**73.8%**	**79.2%**	82.1%	74.1%
0.45	44.8%	86.5%	68.9%	82.3%	82.1%	77.8%
0.46	43.4%	87.6%	68.9%	83.8%	82.1%	79.2%
0.47	39.2%	88.8%	65.6%	86.2%	78.6%	81.9%
0.48	37.8%	91.6%	62.3%	88.1%	78.6%	84.0%
0.49	35.0%	92.1%	59.0%	89.2%	78.6%	85.7%
0.50	32.9%	93.3%	57.4%	90.8%	**78.6%**	**87.4%**
0.51	31.5%	93.3%	55.7%	91.2%	75.0%	87.7%
0.52	30.8%	94.4%	54.1%	91.9%	71.4%	88.4%

Values with the optimum combined sensitivity and specificity are highlighted in bold.
OAHI, obstructive apnoea–hypopnoea index.

could potentially be improved by SpO_2 measures with another sensor focusing on arousals, for example, a mandibular motion device.[23] The ability of NPO to predict OSA in different patient groups, for example, children with severe obesity and neuromuscular disorders also needs further exploration.

Summary

This study provides unique data on the diagnostic accuracy of NPO to predict OSA in non-obese TD children. By presenting sensitivities and specificities for a range of whole number cut-off values, our findings allow clinicians to decide how to use NPO results within their clinical practice. For example, these data may be useful to centres using NPO preoperatively for children with suspected severe OSA secondary to adenotonsillar hypertrophy (as recommended by the British Thoracic Society guideline for diagnosing and monitoring paediatric SDB).[1] Increased use of NPO to diagnose OSA would reduce the burden on healthcare resources given that PSG and CRP are more expensive and limited to specialist centres. Our results suggest that ODI3 and ODI4 are good predictors of moderate-severe OSA in TD children and that NPO may be a suitable alternative to PSG/CRP for diagnosing this. However, low sensitivities to detect mild OSA mean NPO cannot rule out mild OSA. Confirmatory PSG/CRP is therefore needed if NPO is normal in TD children with suspected OSA.

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Não é conhecido se o glicopirrónio ou o formoterol são excretados no leite humano. A administração de Bevespi Aerosphere a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para o bebé. Fertilidade: Considera-se pouco provável que Bevespi Aerosphere, administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes*: Ansiedade, Cefaleia, Tonturas, Boca seca, Náuseas, Espasmos musculares, Infeção do trato urinário, Dor torácica. *Pouco frequentes*: Reações de hipersensibilidade, incluindo erupção cutânea e prurido, Hiperglicemia, Agitação, Irrequietude, Insónia, Tremor, Taquicardia, Palpitações, Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extra-sístoles), Retenção urinária. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: http://www.infarmed.pt/web/infarmed/submissaoram (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351217987373; Linha do Medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado**: Tecnimede - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em outubro 2023. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento comparticipado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 2.0 (outubro 2023).**

Informações essenciais compatíveis com o Resumo das Características do Medicamento
Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirrónio, equivalente a 7,2 µg de glicopirrónio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirrónio, equivalente a 7,7 µg de glicopirrónio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** Posologia: A dose recomendada e máxima é de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. Populações especiais: *Idosos*: Não é necessário qualquer ajuste de dose em doentes idosos. *Compromisso renal:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. *Compromisso hepático:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. *População pediátrica*: Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. Modo de administração: Para utilização por via inalatória. *Instruções de utilização*: De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus FlowVu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Este medicamento não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. Broncospasmo paradoxal: A administração de formoterol/glicopirrónio/budesonida pode produzir broncospasmo paradoxal com sibilos e dispneia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasmo paradoxal. O doente deve ser avaliado e instituído tratamento alternativo, se necessário. Deterioração da doença: Recomenda-se que o tratamento com este medicamento não seja interrompido abruptamente. Se os doentes não considerarem o tratamento eficaz, devem manter o tratamento, mas tem de se procurar aconselhamento médico. O aumento da utilização de broncodilatadores de alívio indica um agravamento do quadro clínico subjacente e justifica uma reavaliação da terapêutica. A deterioração rápida e progressiva nos sintomas da DPOC é potencialmente fatal e o doente deve ser submetido a avaliação médica urgente. Efeitos cardiovasculares: Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas, p.ex. fibrilhação auricular e taquicardia, após a administração de antagonistas dos recetores muscarínicos e simpaticomiméticos, incluindo glicopirrónio e formoterol. Este medicamento deve ser utilizado com precaução em doentes com doença cardiovascular grave não controlada e clinicamente significativa, tal como cardiopatia isquémica instável, enfarte agudo do miocárdio, cardiomiopatia, arritmias cardíacas, e insuficiência cardíaca grave. Recomenda-se também precaução ao tratar doentes com prolongamento do intervalo QTc (QTc> 450 milissegundos para homens ou > 470 milissegundos para mulheres), conhecido ou suspeito, quer seja congénito ou induzido por medicamentos. Efeitos sistémicos com corticosteroides: Podem ocorrer efeitos sistémicos com qualquer corticosteroide inalado, particularmente em doses elevadas prescritas por longos períodos de tempo. Estes efeitos são muito menos prováveis de ocorrer com o tratamento por inalação do que com corticosteroides orais. Os efeitos sistémicos possíveis incluem síndrome de Cushing, manifestações Cushingoides, supressão suprarrenal, diminuição da densidade mineral óssea, cataratas e glaucoma. Devem ser considerados efeitos potenciais na densidade óssea especialmente com a administração de doses elevadas durante longo período de tempo em doentes com fatores de risco coexistentes para osteoporose. Perturbações visuais: Podem ser notificadas perturbações visuais com a utilização sistémica e tópica de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser encaminhado para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, tais como CRSC, que foram notificadas após a utilização de corticosteroides sistémicos e tópicos. Transferência de terapêutica oral: Recomenda-se atenção especial nos doentes que fazem a transição de esteroides orais, uma vez que podem continuar em risco de compromisso da função suprarrenal durante um período de tempo considerável. Os doentes que necessitam de terapêutica com doses elevadas de corticosteroides ou tratamento prolongado com a dose mais elevada recomendada de corticosteroides inalados, podem estar igualmente em risco. Estes doentes podem apresentar sinais e sintomas de insuficiência suprarrenal quando expostos a *stress* grave. Deve ser considerada cobertura adicional com corticosteroides sistémicos durante períodos de *stress* ou cirurgia eletiva. Pneumonia em doentes com DPOC: Tem sido observado um aumento na incidência de pneumonia, incluindo pneumonia que requer hospitalização, nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de risco aumentado de pneumonia com o aumento da dose de esteroide, não tendo sido demonstrado de forma conclusiva nos diversos 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, IMC baixo e DPOC grave. Hipocaliemia: A hipocaliemia potencialmente grave pode resultar da terapêutica com agonistas-β_2. Estes têm o potencial de produzir acontecimentos cardiovasculares adversos. Recomenda-se precaução especial na DPOC grave, pois esse efeito pode ser potencializado pela hipoxia. A hipocaliemia também pode ser potencializada pelo tratamento concomitante com outros medicamentos que podem induzir hipocaliemia, tais como derivados de xantinas, esteroides e diuréticos. Hiperglicemia: A inalação de doses elevadas de agonistas β_2-adrenérgicos pode provocar o aumento da glucose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. Condições coexistentes: Este medicamento dever ser utilizado com precaução em doentes com tirotoxicose. Atividade anticolinérgica: Devido à sua atividade anticolinérgica, este medicamento deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. Os doentes devem ser informados sobre os sinais e sintomas do glaucoma de ângulo fechado e devem ser informados para interromper a utilização deste medicamento e contactarem o seu médico imediatamente, caso algum destes sinais ou sintomas se desenvolvam. Não é recomendada a administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos. Compromisso renal: Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com este medicamento se o benefício esperado superar o risco potencial. Compromisso hepático: Em doentes com compromisso hepático grave, este medicamento só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** Interações farmacocinéticas: Prevê-se que o tratamento em associação com inibidores potentes do CYP3A, por exemplo itraconazol, cetoconazol, inibidores de protéase do VIH e medicamentos que contêm cobicistate, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. Interações farmacodinâmicas: *Outros antimuscarínicos e simpaticomiméticos*: A administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2-adrenérgicos inalados. A utilização concomitante de outros medicamentos beta-adrenérgicos pode ter efeitos potencialmente aditivos; portanto é necessário precaução quando outros medicamentos beta-adrenérgicos são prescritos concomitantemente com formoterol. *Hipocaliemia induzida por* medicamentos: A hipocaliemia pode aumentar a disposição para arritmias em doentes que são tratados com glicosídeos digitálicos. *Bloqueadores β-adrenérgicos*: Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito do formoterol. O uso simultâneo de bloqueadores β-adrenérgicos deve ser evitado, a não ser que o benefício esperado ultrapasse o risco potencial. Se forem necessários bloqueadores β-adrenérgicos, dá-se preferência a bloqueadores β-adrenérgicos cardiosseletivos. *Outras interações farmacodinâmicas*: O tratamento concomitante com quinidina, disopiramida, procainamida, anti-histamínicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procarbazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes*: Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insónia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infeção do trato urinário. *Pouco frequentes*: Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extrassístoles); Irritação da garganta; Broncospasmo; Boca seca; Equimose; Retenção urinária; Dor torácica. *Muito raros*: Sinais ou sintomas de efeitos sistémicos de glucocorticoides, por exemplo supressão suprarrenal; Comportamento anormal. *Desconhecido*: Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: http://www.infarmed.pt/web/infarmed/submissaoram (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351 21 798 73 73; Linha do medicamento: 800 222 444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado**: Tecnimede - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em abril 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento comparticipado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 1.1 (abril 2022).**

ARTIGO ORIGINAL

Poluição atmosférica e consultas respiratórias infantis em cuidados primários: uma revisão sistemática

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RESUMO

Contexto A poluição atmosférica exterior é um fator de risco conhecido para a morbilidade respiratória em todo o mundo. Em comparação com a população adulta, existem menos estudos que analisam a associação entre a exposição a curto prazo à poluição atmosférica e a morbilidade respiratória em crianças em cuidados primários.

Objetivo Avaliar se as crianças num contexto de cuidados primários expostas a poluentes atmosféricos exteriores durante intervalos de curta duração correm um risco acrescido de diagnóstico respiratório.

Métodos Uma pesquisa nas bases de dados Medline, Cochrane Library, Web of Science e Embase até março de 2023. As alterações percentuais ou os rácios de risco com os correspondentes IC de 95% para a associação entre poluentes atmosféricos e doenças respiratórias foram recolhidos de estudos individuais. A avaliação do risco de viés foi realizada com recurso à Escala de Newcastle-Ottawa (NOS) para estudos de coorte ou de caso-controlo e a uma NOS ajustada para estudos de séries cronológicas.

Resultados De 1366 estudos, 14 foram identificados como satisfazendo os critérios de inclusão. A maioria dos estudos apresentou qualidade intermédia ou elevada. Não foi realizada uma meta-análise devido à heterogeneidade da exposição e dos resultados em termos de saúde. No geral, os estudos sobre a exposição a curto prazo a poluentes atmosféricos (monóxido de carbono (CO), dióxido de enxofre (SO_2), dióxido de azoto (NO_2) e partículas ≤10 µm (PM_{10})) foram associados a um aumento das consultas respiratórias infantis em cuidados primários. Em geral, a exposição ao ozono foi associada a uma redução das consultas respiratórias.

Conclusões As evidências sugerem que o CO, SO_2, NO_2, PM_{10} e $PM_{2.5}$ são fatores de risco para doenças respiratórias em crianças em cuidados primários a curto prazo. No entanto, dada a heterogeneidade dos estudos, a interpretação destes achados deve ser feita com cautela.

Número de registo PROSPERO CRD42022259279

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Air pollution increases children's risk of respiratory diseases, including asthma and bronchitis.
- Globally, over 90% of all children live in environments with air pollution levels above the recommended guidelines.
- Particulate matter (PM), ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2) and nitrogen oxides (NOx) have been identified as major causes of health problems in children.

WHAT THIS STUDY ADDS

- This systematic review summarises evidence relevant to this risk within primary care settings—a new perspective compared with prior reviews.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The findings highlights the need for policymakers to ensure safer environments for children.

INTRODUCTION

In 2016, air, water and chemical pollution accounted for nearly 1 million deaths worldwide.[1] Two-thirds of these deaths were in children under the age of 5 years. Research on air pollutants indicates that carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), particulate matter ≤10 µm (PM_{10}) and particulate matter ≤2.5 µm ($PM_{2.5}$) are implicated in numerous respiratory diseases including asthma due to their ability to damage bronchial and pulmonary mucosa.[2] The US National Ambient Air Quality Standards under the direction of the Clean Air Act and the Air Quality Standards commissioned by the European Union developed legislation in their respective regions to limit atmospheric concentrations of CO, SO_2, NO_2, O_3, PM_{10} and $PM_{2.5}$.[3] Despite the legislation, 93% of all children and about 630 million children under 5 years are exposed to higher levels of air pollution than recommended by these air quality standards.

Infants and children are more likely to manifest adverse respiratory symptoms from air pollution exposure due to a number of factors.[4] For instance, the immature immune and respiratory system of a child can increase the risk of lung tissue damage, which in turn delays lung growth and increases susceptibility to conditions like asthma.[1 5] Compared with adults, children are exposed to higher doses of ambient air pollutants because they spend more time outdoors and breathe about 50% more air per kilogram of body weight.[6 7]

For the past two decades, several (systematic) reviews have pooled together findings on the association between childhood respiratory diseases and air pollution. For example, a 2012 literature review of 30 studies showed adverse effects of PM_{10} and NO_2 on children's respiratory symptoms and lung function.[8] Furthermore, negative associations were stronger in children with pre-existing respiratory conditions compared with healthy children. Atkinson et al included 110 time series studies of daily mortality and hospital admissions.[9] Their summary estimates showed that for each 10 µg/m^3 increase in $PM_{2.5}$, the risk of hospitalisation for asthma or respiratory symptoms increased by 2% in children aged 0–14 years. Bowatte et al showed that when exposed to moderate road traffic emission, children were significantly more likely to report wheezing (OR 1.26; 95% CI 1.13 to 1.42) and bronchodilator use (OR 1.20; 95% CI 1.04 to 1.38) compared with

children exposed to little or no road traffic emission.[6] Zheng et al performed a meta-analysis and showed that children were at a higher risk of emergency room visits or hospital admissions when exposed to air pollutants.[2]

Given that respiratory symptoms are among the top three reasons children aged 0–17 years consulted their general practitioner (GP), it calls for an in-depth analysis of the available literature with respect to this patient population and setting.[10] However, despite the significant health and economic impact of air pollution exposure, little is known about the short effect of air pollution on the frequency of respiratory symptoms in children who visit their GP.[11] The objective of this review was to evaluate whether children in a primary care setting exposed to outdoor air pollutants are at (increased) risk of respiratory diagnoses.

METHODS

The protocol for this review was registered with PROSPERO under registration number CRD42022259279. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to report our findings. The search strategy was conducted in the following manner: first, we formulated the main question using the Population, Exposure, Comparator and Outcome statement. Second, we performed a literature search of both electronic databases and references from retrieved papers. We systematically searched literature published through 12 March 2023. Four databases identified were: Embase (embase. com), Medline ALL (Ovid), Web of Science Core Collection (Web of Knowledge) and Cochrane Central Register of Controlled Trials (Wiley). No limits to publication year or language were imposed.

Review or research papers with no original data in their results were excluded. The following additional exclusion criteria were applied: studies using pregnant subjects or animals; studies that evaluated indoor air pollutants; research on non-respiratory health outcomes; case reports; policy publications or studies published in abstract form only. Two authors (MSF and ERvM) independently screened titles and then performed a full-text review of studies that met inclusion criteria. In the event that a full text was not available, MSF contacted the original authors using the correspondence address on the publication. If no response from the author was received, the article was excluded from the review. Reference lists of eligible studies were included in the list for full-text review. Any disagreement on inclusion was resolved by discussion and, if no consensus was reached, a third reviewer (EdS) was consulted.

Study data were extracted including publication year, study design, study country, study population (children aged between 0 and 18 years who visited a primary care practitioner), air pollu-tants and respiratory outcomes. Effect measures and their 95% CIs that were extracted from studies included percentage (%) change in respiratory outcomes per increase in air pollutant level, risk/relative ratios (RRs), ORs, excess relative risk (ERR) and HRs. Where applicable, effect measures were pooled for a fixed increment in pollutant concentration (per 1 µg/m^3); other reported quantities or units such as parts per billion and parts per million were converted using the previously published formulas.[12–15]

Evaluation criteria

We assessed the methodological quality of the studies included and the possibility of bias using the Newcastle–Ottawa Scale (NOS) for case–control studies and cohort studies. The NOS for cohort studies measures three dimensions (selection, comparability and outcome). In the NOS for case–control studies, the outcome dimension is replaced by exposure. A study can be awarded a minimum of one star for each numbered item within the selection, outcome or exposure categories and a maximum of two stars in the comparability category. A study can therefore receive a total of nine stars. A study with a

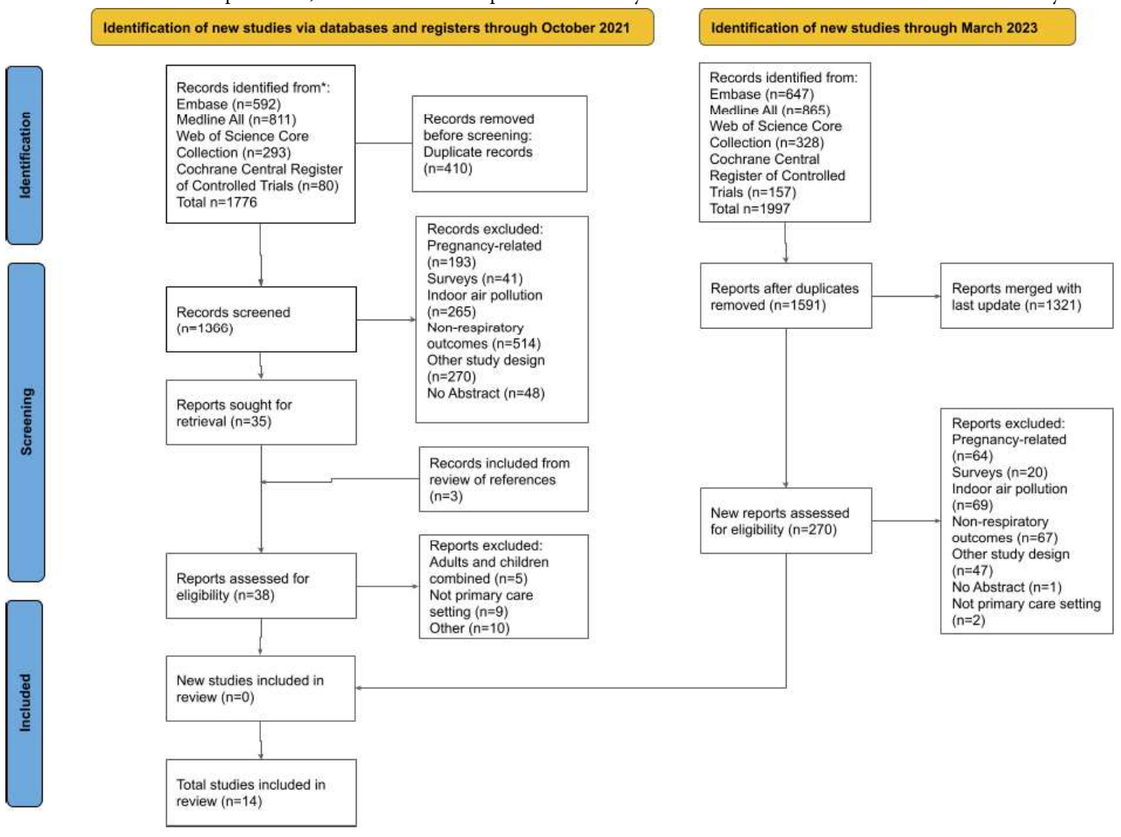

Figure 1 Flow chart of search results included in the review.

Table 1 Characteristics of studies about the effects of exposure to ambient air pollutants on childhood respiratory diseases in primary care settings

ID	Author (year), country	Study design	Study population (age, years); setting; study period	Sample size (n)	Respiratory outcome (URD, LRD or both)	Monitoring sources; sites (n)	Air pollutants	Exposure duration (short-term, long-term or both)	Effect measure	Adjustment variables	Study quality
1	Ashworth *et al*[23] (2021), UK	TS	Children (0–7) & adults (18–64, >64); PC; 2009–2013	1.16 million	Both	Air Quality Networks: NO_2 (130); PM_{10} (115); O_3 (62); $PM_{2.5}$ (104)	NO_2, O_3, $PM_{2.5}$, PM_{10}	Both	% change	DOW, T, H, IMD	High
2	Martin *et al*[21] (2018), ES	C	Children (0–14); PC; 2013–2015	52 322	URD	Madrid City Council website (NA)	SO_2, NO_2, CO, O_3, $PM_{2.5}$, PM_{10}	Long-term	RR	Not disclosed	Intermediate
3	Lindgren *et al*[27] (2013), SE	C	Children (0–6); PC; 2005–2010	26 128	Both	Emission database (NA)	NO_x	Both	HR	Sex, ETS, BF, PA, PO, PE, YOB	Intermediate
4	Kukec *et al*[20] (2013), SL	TS	Children (1–11); PC; 2000–2002	NA	Both	Zagorje (1); Trbovlje (1); Hrastnik (1)	SO_2, NO_2, O_3, PM_{10}	Short-term	IRR	S, T, H, Infl, DOW	Intermediate
5	Lai *et al*[8] (2012), UK	C-C	Children (5–16); PC; 1999–2004	8726	LRD	National air archive, Aberdeen Scotland (NA)	SO_2, NO_2, CO, O_3, PM_{10}	Short-term	% change	PH, S	Intermediate
6	Portnov *et al*[19] (2011), IL	C	Children (6–14); PC; 2008–2009	3922	LRD	Air quality monitoring stations (14)	PM_{10}, SO_2	Long-term	OR	Not disclosed	Poor
7	Larrieu *et al*[28] (2009), FR	TS	Children (0–15) & adults (>65); PC; 2000–2006	600 000	Both	Air quality monitoring stations (4)	PM_{10}, NO_2, O_3	Short-term	ERR	S, T, Infl, pollen, DOW, PH	Intermediate
8	Babin *et al*[29] (2008), USA	C	Children (0–4, 5–12, 13–20) & adults (21–49, 50–64, >65); PC, H&O; 1994–2005	NA†	LRD	Environmental Protection Agency sites (6)	$PM_{2.5}$, PM_{10}, O_3	Short-term	% change	S, T, dew, DOW	Intermediate
9	Hwang and Chan[16] (2002), TW	TS	Children (0–14) & adults (15–64, >65); PC; 1998–1999	278 000	LRD	Taiwan Air Quality Monitoring Network (59)	SO_2, NO_2, CO, O_3, PM_{10}	Short-term	% change	WD, WS, T, dew	Intermediate
10	Hajat *et al*[26] (2002), UK	TS	Children (0–14) & adults (15–64, >65); PC; 1992–1994	295 740	URD	Monitoring stations across London (11)	SO_2, NO_2, CO, O_3, PM_{10}	Short-term	% change	S, DOW, PH, Infl, T, pollen	High
11	Hajat *et al*[30] (2001), UK	TS	Children (0–14) & adults (15–64, >65); PC; 1992–1994	253 635	URD	Monitoring stations across London (11)	SO_2, NO_2, CO, O_3, PM_{10}	Short-term	% change	S, T, H, Infl	High
12	Hajat *et al*[31] (1999), UK	C	Children (0–14) & adults (15–64, >65); PC; 1992–1994	295 740	Both	Monitoring stations across London (11)	SO_2, NO_2, CO, O_3, PM_{10}	Short-term	% change	S, T, H, Infl	High
13	Ostro *et al*[22] (1999), CL	TS	Children (0–2, 3–15); PC; 1992–1993	153 548	Both	Metropolitan Environmental Health Service (4)	PM_{10}, O_3	Short-term	% change	S, T, H, H5PM; CSD, DOW, Infl	High
14	Medina *et al*[32] (1997), FR	C	Children (0–14) & adults (15–64); PC; 1991–1995	6.1 million	LRD	Paris Air Pollution Network (38)	SO_2, NO_2, CO, O_3, PM_{10}	Short-term	RR	T, pollen, DOW, PH, Infl	High

*2191 days observed.
†61 218 annual general care visits.
BF, breast feeding; C, cohort; C-C, case–control; CSD, coldest 5% of the days; CL, Chile; CO, carbon monoxide; dew, daily average dew point temperature; DOW, day of the week; ERR, excess relative risk; ES, Spain; ETS, environmental tobacco smoke; FR, France; H, humidity; H&O, hospital and outpatient care; H5PM, days of highest 5% PM_{10}; IL, Israel; IMD, Index of Multiple Deprivation; Infl, influenza; IRR, incidence risk rate; LRD, lower respiratory tract disease; NA, not available; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; PA, parental age; PC, primary care; PE, parental education; PH, public holidays; PM_{10}, particulate matter ≤10 µm; $PM_{2.5}$, particulate matter ≤2.5 µm; PO, parental origin; RR, relative risk; S, seasonality; SE, Sweden; SL, Slovenia; SO_2, sulfur dioxide; T, temperature; TS, time series; TW, Taiwan; URD, upper respiratory tract disease; WD, wind direction; WS, wind speed; YOB, year of birth.

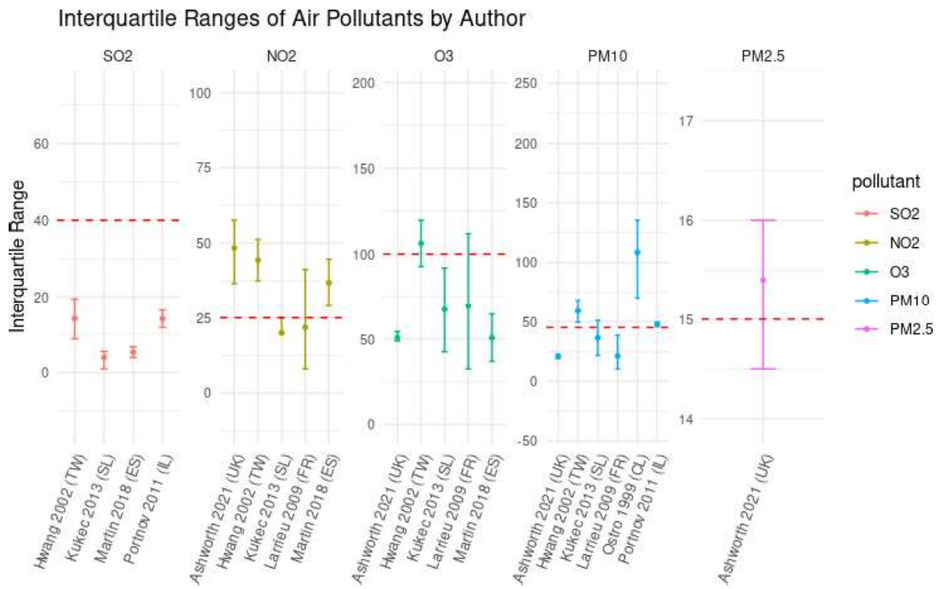

Figure 2 Distribution of air pollution concentration per study. CL, Chile; ES, Spain; FR, France; IL, Israel; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter ≤2.5 µm; PM_{10}, particulate matter ≤10 µm; SL, Slovenia; SO_2, sulfur dioxide; TW, Taiwan.

NOS score of 1–3, 4–6 or 7–9 was evaluated as poor, intermediate or high quality, respectively. For time series analysis, we used an adjusted NOS score previously published in other systematic reviews.[16,17] The adjusted NOS evaluates three components: (1) the validation of respiratory outcome occurrence (0–1 point), (2) the quality of air pollutant measurements (0–1 point) and (3) the extent of adjustment for confounders (0–3 points). A study with an adjusted NOS score of 0–1, 2–3 or 4–5 received an overall quality of poor, intermediate or high, respectively.

Concerning the validation of respiratory outcomes, we considered the diagnosis to be validated if it was coded according to the International Classification for Primary Care (ICPC) or International Classification of Diseases (ICD).

We identified eight effect measures which we aggregated into two groups (change in outcome per unit µg/m³ air pollutant and change in outcome per IQR/percentile change in air pollutant). Each group contained the following items: outcome type (upper respiratory, lower respiratory or both), exposure duration (short-term or long-term), pollution type (CO, SO_2, NO_2, O_3, $PM_{2.5}$ and PM_{10}), effect size and 95% CI (lower limit and upper limit). A meta-analysis was not performed due to the heterogeneity of the study designs and outcomes.

RESULTS

We identified 1366 unique articles, of which 1331 were excluded based on title and abstract screening (figure 1). We screened 35 full texts and identified 3 articles from article references. A total of 14 articles were included in this review. Characteristics of these studies are shown in table 1. The majority were conducted in Europe and the most common type of study design was time series. Short-term exposure to air pollutants was frequently reported.

Air pollutants

The most common air pollutants encountered in the review were SO_2, NO_2, O_3 and PM_{10}. Compared with the recommended air quality guidelines (AQGs) by the WHO, the majority of studies had air pollutant levels far below the recommendations (figure 2). For instance, the mean SO_2 levels in four studies were substantially below the recommended minimum level of 40 µg/m³.[18–21] A total of five studies had mean O_3 levels below the AQG recommendations (100 µg/m³). With regard to NO_2 and PM_{10}, most studies had higher mean concentration values than their respective AQG recommendations. Only one study reported on $PM_{2.5}$, and the mean value was similar to the recommended AQG.

Lower respiratory diseases

Five of the six studies suggested an increased % change in consultations for lower respiratory tract diseases (LRDs) after short-term exposure to CO, SO_2, NO_2 and/or PM_{10}. Throughout the year, asthma diagnosis was sensitive to short-term exposure to CO, SO_2, NO_2 and PM_{10}. Two studies suggested a significantly increased % in daily visits for asthma with higher levels of O_3. Contrary to this, one study found that short-term exposure to O_3 was predominantly associated with a reduction in asthma consultations.

With regard to short-term exposure to PM_{10}, two of the six studies that reported exclusively on LRD including asthma showed an increase in RR of 1.32 (95% CI 0.82 to 2.13) in house calls. Furthermore, in a study performed in Chile, a 50 µg/m³ change in PM_{10} was associated with more frequent clinic visits of 2.5% (95% CI 0.2% to 4.8%) in younger children compared with 3.7% (95% CI 0.8% to 6.7%) in older children.[22]

Upper respiratory tract diseases

Three time series reported on upper respiratory tract diseases (URDs), of which, one was limited to allergic rhinitis. Specifically, this latter study demonstrated that an increase in consultations for allergic rhinitis was due to short-term exposure to SO_2, 24.5% (95% CI 14.6% to 35.2%), NO_2, 11.0% (95% CI 3.8% to 18.8%), O_3, 11.4% (95% CI 4.4% to 19%) and PM_{10}, 10.4% (95% CI 2% to 19.4%) (figure 3).

Upper and lower respiratory diseases

Two time series examined the effect of air pollution on both lower and upper respiratory diseases. Within one of the most polluted regions in Slovenia, the RRs of daily first consultations for all respiratory diseases including influenza and pneumonia were 0.986 (95% CI 0.977 to 0.995) for SO_2, 0.998 (95% CI 0.996 to 1.001) for O_3 and 1.004 (95% CI 1.002 to 1.006) for PM_{10} levels (figure 3).

Funnel plots for air pollutant exposure and respiratory outcome effect sizes are presented in figure 4. The visual inspection of the funnel plots showed some indications for publication bias. For short-term exposure to O_3 and NO_2, the presence of publication bias was confirmed by Egger's test. A funnel plot for $PM_{2.5}$ was not applicable due to small numbers.

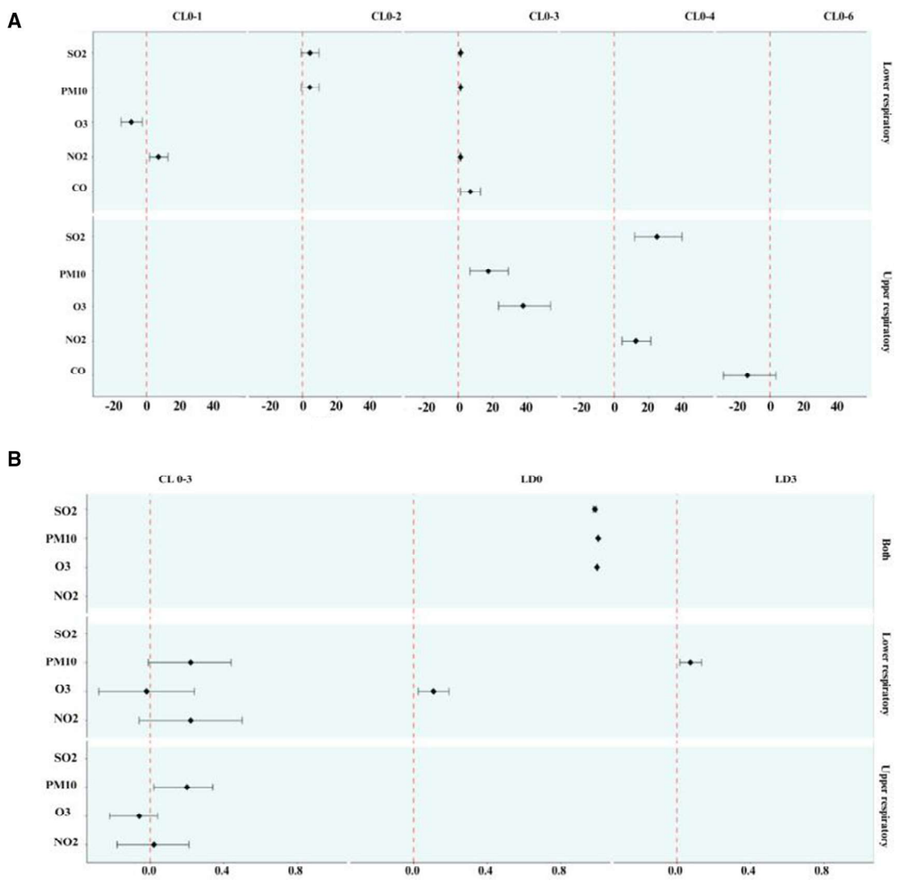

Figure 3 (A) Percentage change in respiratory outcome per IQR or percentile increase of air pollutant according to cumulative lag (CL). (B) Percentage change in relative risk (RR) or incidence risk rate (IRR) of respiratory outcome per µg/m³ increase in air pollutant according to lag day (LD). NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter ≤10 µm; SO_2, sulfur dioxide.

DISCUSSION

In the current systematic review of 14 studies conducted in 10 countries, we evaluated data on outdoor air pollution and respiratory diseases in children. Most short-term exposure studies reported a positive association between air pollution concentrations (specifically for CO, NO_2, SO_2 and PM_{10} air pollutants) and children with respiratory morbidity in primary care settings. Two studies that reported on the effect of $PM_{2.5}$ levels showed a slight increase in consultation rates for respiratory diseases. With regard to O_3 exposure, most studies reported a negative association between short-term exposure and lower respiratory diseases. O_3 concentrations are typically higher in rural areas compared with urban areas due to traffic emission and industrial activities. All studies in this

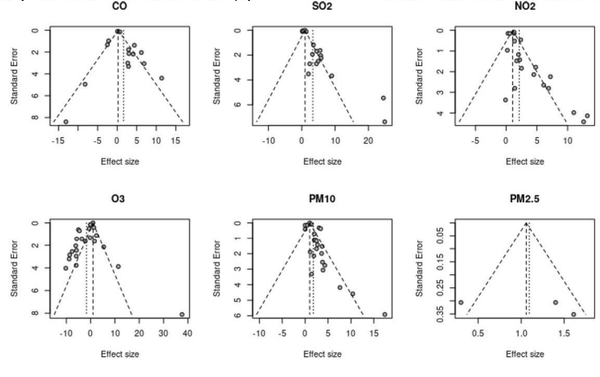

Figure 4 Funnel plots for short-term air pollutant exposure and respiratory outcome effect sizes. NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, particulate matter ≤2.5 µm; PM_{10}, particulate matter ≤10 µm; SO_2, sulfur dioxide.

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review were in urban settings. Another explanation for the interaction between O_3 and reduced consultations for respiratory diseases is better access to healthcare in urban areas compared with rural settings. In one study, short-term exposure to O_3 was associated with increased prescription of preventive inhaler medication without adjusting for NO_2.[23]

Two meta-analyses published before 2021 documented positive associations for short-term exposure to air pollutants and respiratory diseases. They both included studies that reported their findings from hospitalised children with asthma and/or wheeze.[2,24] One of the systematic reviews included 87 studies and the other 13 with varying methodology. However, the pooled RRs and ORs were similar. A recent systematic review on 11 time series and 6 case-crossover studies reported a positive association between daily levels of air pollutants and hospitalisation due to pneumonia in children.[25]

For the studies that investigated short-term effects of air pollution on respiratory morbidity, interpretation should be done cautiously. In particular, the definition of URD and LRD comprised broad spectrum of diagnoses and only one study excluded allergic rhinitis from their URD definition.[26] Furthermore, it is not clear whether exposure at lag 0–7 days triggers an existing respiratory condition or if these are new occurrences of events. In our review, two studies reported on new cases as first dispensed inhalers or first consultation for respiratory disease, while the rest did not specify whether children had pre-existing respiratory conditions.[20 27] In addition, no study reported on functional assessment for respiratory illness by a GP or nurse. One study investigated the association between preventer or inhaler medication with short-term and long-term exposure to air pollutants.[23]

Studies varied in design, outcome definition, exposure assessment and the number of studies for some pollutants were limited in order to perform a meta-analysis. Our risk of bias assessment suggested that half of the studies have an intermediate level of risk of bias, but overall, the pattern of results does not suggest that the biases would have produced a false association. The most common form of bias was determined to be from the type of exposure and misclassification of respiratory disease outcomes. Only one study in our review adjusted for personal factors (specifically Index of Multiple Deprivation) and found similar results compared with studies without adjustment for personal factors.

To our knowledge, this is the first comprehensive literature review on air pollution effects and childhood respiratory diseases in a general practice setting. One strength is that most of the studies were performed in developed countries and thus we can assume some generalisability of the current evidence to similar regions. However, some limitations should be acknowledged.

First, the included studies differed markedly in outcome assessment (for instance, the definition of respiratory diseases), exposure assessment (for instance, measurements from air monitoring stations vs spatial-statistical model), effect measures (for instance, % change in number of respiratory consultations vs incidence risk rate or %ERR with varying unit increase of air pollutants) and exposure period (for instance, lag days for short-term exposure). Second, many of the findings presented in the review consisted of data from the same cohort of children. Third, most studies focused on SO_2, NO_2, O_3 and PM_{10} and a few investigated the effects of $PM_{2.5}$ on respiratory outcomes. Fourth, some studies objectively defined respiratory diseases using ICD or ICPC classifications and others did not use such coding systems. In the latter case, this may lead to misclassification of outcomes and thereby underestimating the effect estimates. Fifth, the number of covariates differed among the studies and several important factors such as seasonality, influenza and pollen were not adjusted in most studies, hence limiting interpretation of the findings due to residual confounding. Sixth, the vast majority of studies used single-pollutant models to generate their effect estimates; however, it is known that air pollutants correlate with each other and the respiratory effects of one pollutant can be masked or dominated by other pollutant(s).

CONCLUSION

The evidence we reviewed suggests an association between short-term exposure to air pollution with respiratory diseases in children in primary care. This association was seen even when air pollutant concentrations (in particular for SO_2 and PM_{10}) were below the WHO-recommended AQG levels. Contrary to the literature, four studies observed an inverse relationship between O_3 and respiratory diseases. This could be explained by either less outdoor activities during periods of high temperature or increased use of preventive inhalers and better access to healthcare in urban areas. We found few data on short-term exposure to $PM_{2.5}$ and respiratory diseases. $PM_{2.5}$ is considered as fine fractions that can penetrate deeper in the airways in comparison with other air pollutants. Hence, it is important to understand the potential biological mechanisms of $PM_{2.5}$ in the lungs and systemic inflammatory processes induced as it penetrates cellular barriers. Furthermore, given the number of children at risk of exposure to $PM_{2.5}$, the population health implications can be substantial. The findings from this review suggest that a multidisciplinary approach to prevent respiratory morbidity due to air pollution is required so that policymakers, parents and health professionals alike can act in a timely manner and accordingly.

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Contributors MSF designed the review protocol, analysed the data, drafted and revised the review. MSF and ERvM performed the data extraction and risk of bias assessments. ABu, PB, AB, EdS and ERvM contributed to critically reviewing and revising the article and approved the final draft. MSF is the guarantor of the work.
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ARTIGO ORIGINAL

Epidemiologia global da colonização assintomática de *Staphylococcus aureus* resistente à meticilina no trato respiratório superior de crianças jovens: uma revisão sistemática e uma meta-análise

Liuyue Yang,[1] Priyanga Dharmaratne,[1] Chendi Zhu,[1] Dulmini Nanayakkara Sapugahawatte,[1] Nannur Rahman,[1,2] Nilakshi Barua,[1] Carmen Li,[1] Kin On Kwok,[3,4] Mingjing Luo,[5] Veranja Liyanapathirana,[6] Margaret Ip[1,7]

RESUMO

Objetivo Estimar a prevalência global da colonização assintomática e determinar os fatores de risco associados, a resistência aos antibióticos e os genótipos de Staphylococcus aureus resistente à meticilina (SARM) no trato respiratório superior de crianças jovens.

Desenho Foram pesquisadas quatro bases de dados bibliométricas para publicações entre 2010 e 2022, de acordo com o protocolo registado em PROSPERO. Foram incluídos estudos transversais ou de coorte que descrevessem a prevalência de colonização assintomática de S. aureus e SARM em crianças jovens. A extração e a análise dos dados foram realizadas por dois revisores, de forma independente e de acordo com a declaração Preferred Reporting Items for Systematic Reviews and Meta-Analyses de 2020. A prevalência agregada foi estimada utilizando um modelo de efeitos aleatórios.

Contexto e estudos

Incluímos estudos em que as crianças sem infeção do trato respiratório ou infeção estafilocócica foram recrutadas na comunidade, em instituições infantis (ou seja, creches, jardins de infância, infantários e pré-escolar) e em visitas a centros de saúde e que foram avaliadas relativamente à colonização assintomática por S. aureus e SARM.

Medições dos resultados principais A prevalência agregada de colonização assintomática de S. aureus e SARM em crianças jovens a nível mundial.

Resultados Nesta revisão sistemática e meta-análise de 21 416 crianças jovens, a prevalência global agregada da colonização assintomática por S. aureus foi de 25,1% (IC 95% 21,4 a 28,8) e a colonização por SARM foi de 3,4% (IC 95% 2,8 a 4,1). Os clones das estirpes de SARM incluíram SARM associado aos cuidados de saúde, SARM associado à comunidade e SARM associado ao gado.

Conclusão O presente estudo fornece evidências do aumento da colonização por SARM a nível mundial entre crianças jovens, sublinhando o papel crítico dos portadores assintomáticos na transmissão de SARM e a necessidade de medidas de controlo.

Número de registo PROSPERO CRD42022328385.

Key messages

What is the key question?

▶The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) colonisation and infection was 2.8% (95% CI 1.6 to 4.0) among children (0–5 years old) between 2000 and 2010 reported in a meta-analysis and systematic review. The prevalence of MRSA among young children was higher than among healthy adults (0.8%; 95% CI 0.0 to 17.5), which may be due to their immature immune system and interaction with asymptomatic MRSA carriers.

What is the bottom line?

▶Asymptomatic MRSA colonisation among young children may have increased in the last decade. Available studies were mostly regional, and more data on a global scale are needed. To the best of our knowledge, this study is the first systematic review and meta-analysis on the global prevalence and epidemiology of asymptomatic MRSA colonisation in young children.

Why read on?

▶Public health policymakers should take asymptomatic MRSA transmission into consideration to implement antibiotic regulatory and infection control measures that will limit the spread, and protect children.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been officially recognised as a significant pathogen with high antimicrobial resistance, as outlined in the 2017 global priority pathogens list published by the WHO.[1] Community-associated MRSA (CA-MRSA) infection is often reported among healthy children under 6 years of age.[2]

Colonisation is defined as the presence of bacteria on the human body's surface (eg, airway, skin and mouth) without displaying disease symptoms and is regarded as a prerequisite for infection.[3] However, many publications confuse 'colonisation' with 'infection'.[3] Therefore, 'asymptomatic colonisation' is adopted to distinguish it from infection, as defined by Chisholm, Campbell.[4]

The respiratory tract of humans, particularly the anterior nares, serves as the primary ecological reservoir for *S. aureus*.[5] *S. aureus* can adhere and multiply in the nose and transmit among the human nose via hands and air.[6] Individuals who are persistently colonised by MRSA are at an increased risk for MRSA infection.[7] The rate of invasive CA-MRSA infection cases among children rose from 1.1 cases per 100 000 children in 2005 to 1.7 cases per 100 000 children in 2010 according to a population-based active surveillance programme in the USA, with a modelled yearly increase of 10.2% (95% CI 2.7 to 18.2).[8] Most studies were conducted nationally, while aggregate global data on asymptomatic MRSA colonisation among children are lacking. Hence, the role of 'asymptomatic MRSA colonisation' in MRSA transmission could be underestimated in surveillance programmes and in developing policies and programmes on infection control.[4] Thus, understanding the prevalence and epidemiology of asymptomatic MRSA colonisation in the upper respiratory tract of young children could provide better evidence for developing infection control and prevention strategies locally and globally.

To the best of our knowledge, this is the first systematic review and meta-analysis focused on the global prevalence and epidemiology of asymptomatic MRSA colonisation in young children. The study aimed to identify the prevalence of *S. aureus* and MRSA asymptomatic colonisation and risk factors associated with asymptomatic MRSA colonisation in the upper respiratory tract of young children and to characterise the antibiotic resistance and genetic characteristics of relevant MRSA isolates.

METHOD

The systematic review and meta-analysis followed the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement[9] and registered on PROSPERO.

Searching strategies and eligible criteria

All review authors collaboratively developed the search strategies (online supplemental appendix I) for publications. A comprehensive publication search was conducted on Medline, Embase, Web of Science and CINAHL on 3 March 2022. All the records were exported to Covidence (https://www.covidence. org/). Studies had to report prevalence data on both *S. aureus* and MRSA in young children to be eligible, and other eligibility criteria are listed in online supplemental appendix II.

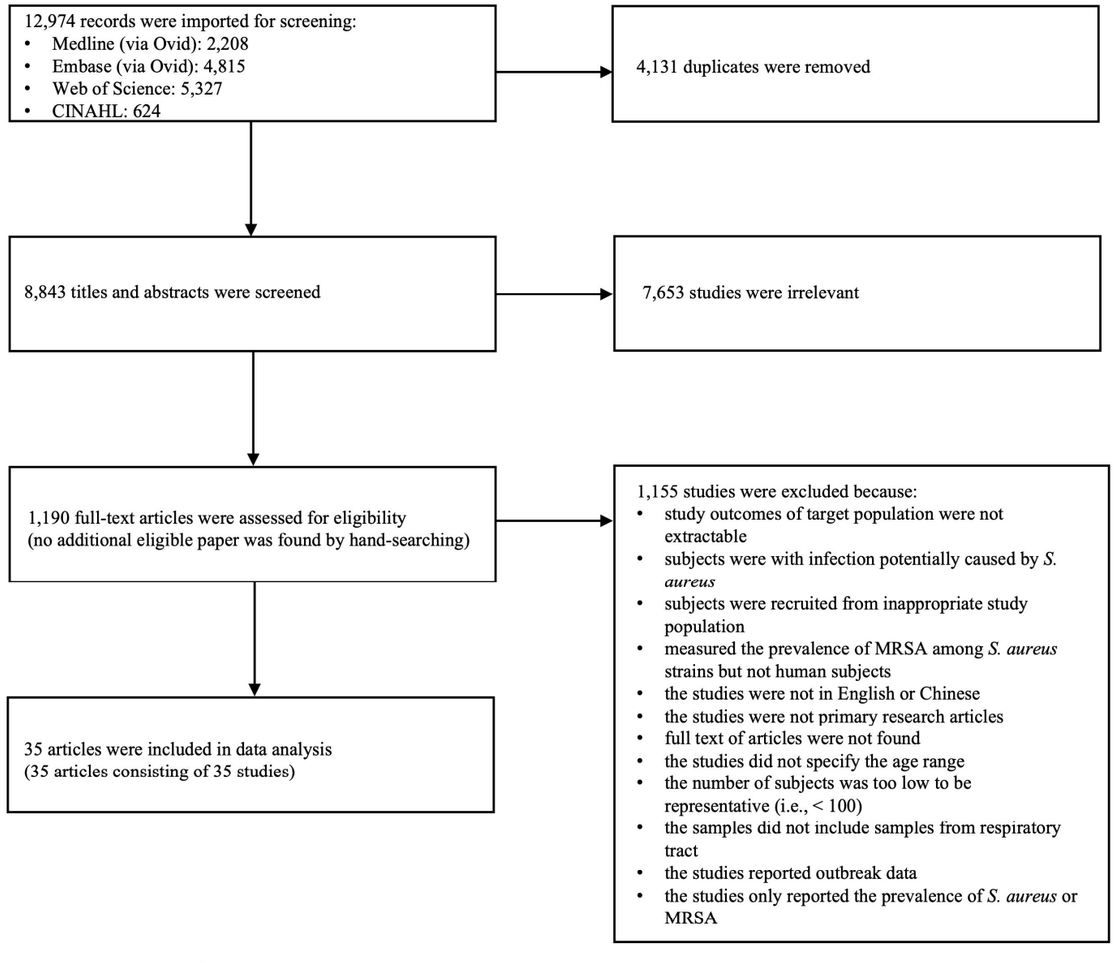

Figure 1 Flow diagram for publications screening. MRSA, methicillin-resistant *Staphylococcus aureus.*

Data extraction

A data collection form (online supplemental appendix III) was designed for data extraction. Missing data were extracted from figures if possible. The primary outcomes of interest were the prevalence of asymptomatic *S. aureus* and MRSA carriage among young children without infection. For cohort studies, if specimens for *S. aureus* and MRSA screening were collected from a subject more than once, only the first screening outcomes were extracted. As for the secondary outcomes, significant risk factors for asymptomatic colonisation, antibiotic resistance and genetic characteristics of MRSA in young children were extracted. Basic information about the studies was also extracted, including author names, publication year, country/continent, economic status of countries, screening setting, study design, sampling sites, total number of target subjects, age/age group, health status, *S. aureus* screening method, MRSA confirmation method and whether combining pre-enrichment (ie, broth enrichment to enhance the sensitivity of detection) before *S. aureus* detection.

Bias assessment and data analysis

The risk of bias in publications was assessed using Joanna Briggs Institution (JBI) standardised critical appraisal checklist for both cross-sectional and cohort studies. The checklist comprised nine questions to determine the possible bias in the design, conduct, and analysis experiment.[10]

The 'meta' package[11] in R software (V.4.1.2) was employed for all the statistical analyses. As a binary primary outcome, the overall

► Additional supplemental material is published online only. To view, please visit the journal (http://dx.doi.org/ 10.1136/ archdischild-2023-326124).

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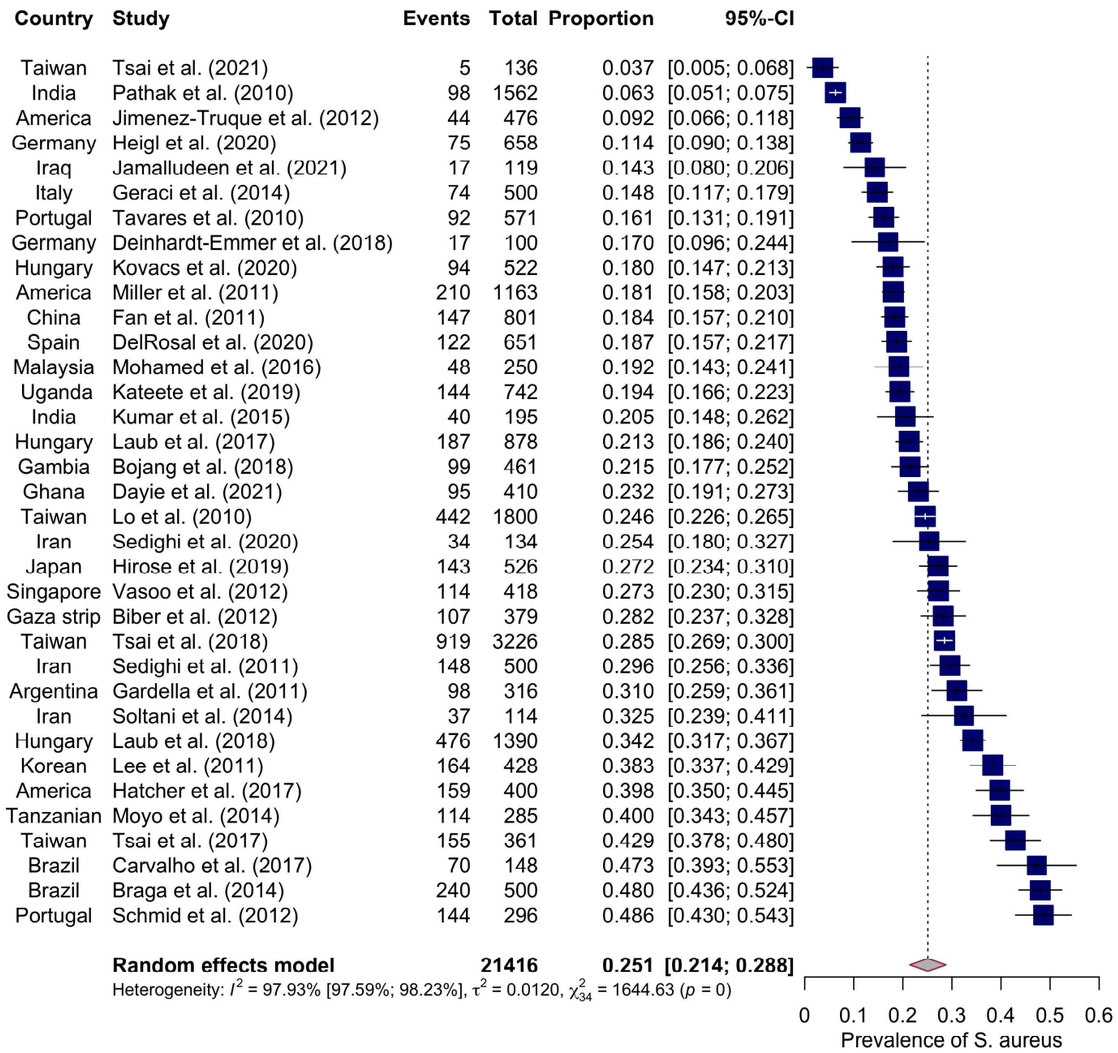

Figure 2 Forest plot for the prevalence of *S. aureus* asymptomatic colonisation (n=35).

pooled prevalence and the 95% CI for asymptomatic *S. aureus* and MRSA colonisation were calculated with a random-effects model and visualised in forest plots. Statistical heterogeneity between studies was assessed by I^2 statistics and interpreted according to the Cochrane Collaboration.[12] The possible causes of heterogeneity were examined using subgroup analysis based on certain potential independent factors. The estimated prevalence of each subgroup was reported. As part of the secondary outcomes, the available quantitative data on antibiotic resistance and genetic characteristics of MRSA isolates were analysed using a random effects model. A p-value less than 0.05 was considered statistically significant.

RESULTS

Study selection and data extraction

A total of 12 974 publication records were initially collected (figure 1). Of these, 8843 unique records were screened by title and abstract, and 1190 were subjected to full-text screening. After excluding those not fulfilling the inclusion criteria, 35 articles were identified (34 peer-reviewed articles and one letter to the editor).

The prevalence of *S. aureus* and MRSA was extracted from all included publications. Of the 35 studies,[13–47] seven[13 15 17 20 23 24 27] reported significant risk factors or predictors of asymptomatic MRSA colonisation in young children.

Study characterisation

The included studies were conducted from 2004 to 2019 in 22 countries on five continents (detailed in online supplemental appendix IV). Among them, non-duplicate subjects from three publications from Taiwan were eligible.[44–46] Most included studies were cross-sectional studies (31/35), while the remainder were cohort studies. *S. aureus* and MRSA screening were conducted among children from children's institutions (20/35), followed by healthcare centres and communities. A total of 18 190 subjects were young children (0–8 years old) without respiratory infections or other potential infections caused by *S. aureus* infections.

From the studies, only five had more than 1000 subjects, and the majority (20/35) had fewer than 500 subjects. Most screening specimens (23/35) were mainly collected from nares only and followed by nasopharynx only. Moreover, the risk of bias in all included studies assessed with the JBI standardised critical appraisal checklist for included studies was with an overall score (yes%) higher than 60%, which was with acceptable publication quality (detailed in online supplemental appendix V).

Overall pooled prevalence

All studies (n=35) were included in the pooled prevalence analysis using a random effects model. The pooled prevalence of asymptomatic *S. aureus* colonisation was 25.1% (95% CI 21.4 to 28.8) (figure 2). The prevalence of each study derived largely from 3.7% to 48.6% with a significant degree of statistical heterogeneity (I^2: 97.9% (97.6 to 98.2); p≤0.0001). The highest prevalence was observed in studies conducted in Portugal (48.6%),39 followed by Brazil (48.0% and 47.3%).15 16 For MRSA, the pooled prevalence was 3.4% (95% CI 2.8 to 4.1) (figure 3). The prevalence of each study ranged from 0.0% to 29.4% with significant heterogeneity (I^2: 96.7% (96.0 to 97.2); p≤0.0001). The highest prevalence of asymptomatic MRSA colonisation was reported in Taiwan (29.4%),[44] followed by Iran (16.7%).[42]

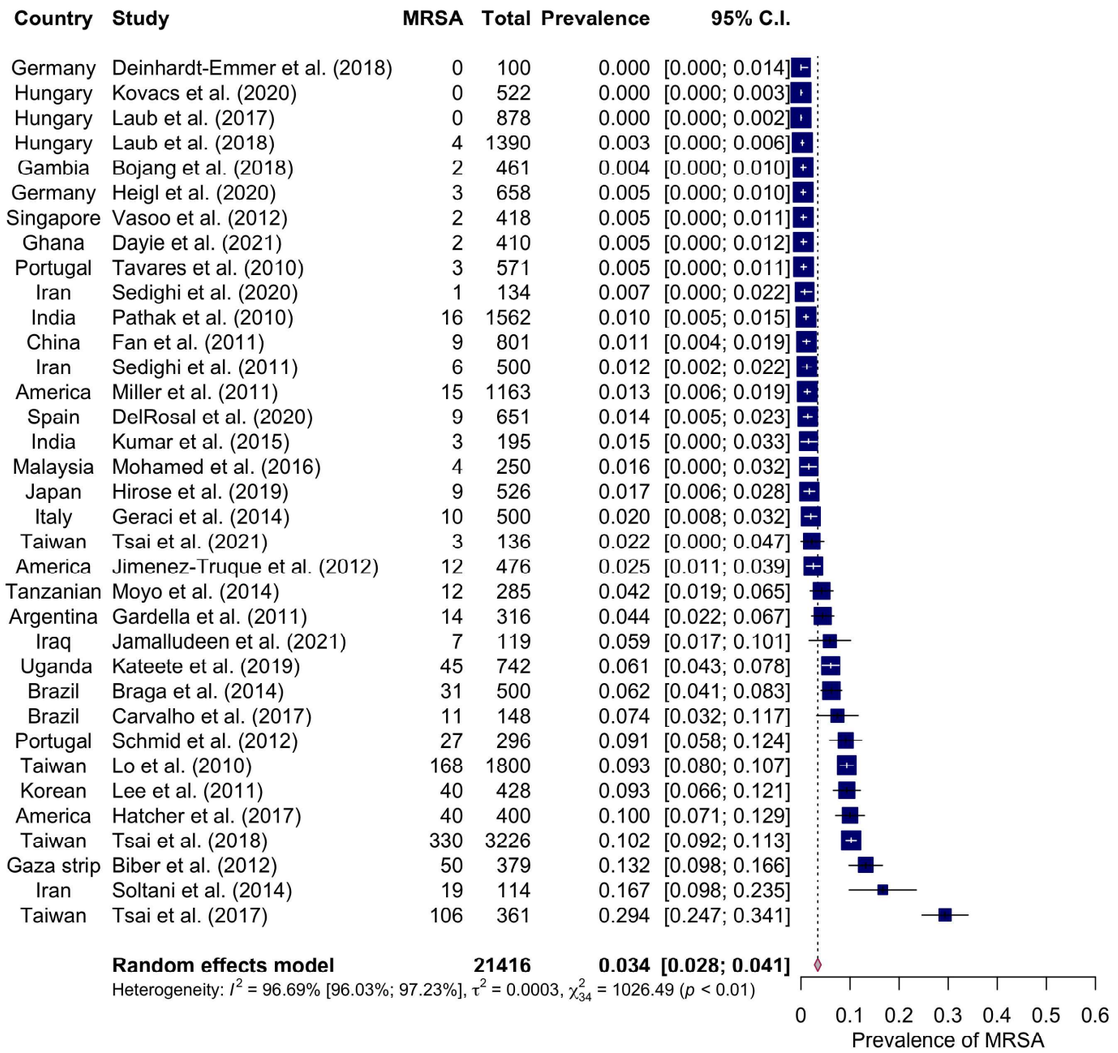

Figure 3 Forest plot for the prevalence of MRSA asymptomatic colonisation (n=35). MRSA, methicillin-resistant *Staphylococcus aureus*.

Subgroup analysis for the prevalence of MRSA

Subgroup analyses for the prevalence of asymptomatic MRSA colonisation were conducted using nine independent factors (online supplemental appendix VI). Among them, the pooled prevalence of each subgroup differed significantly when the subgroups were divided by continent (p<0.0001), screening setting (p<0.0001) and age group (p<0.0001). As shown in figure 4, MRSA prevalence was higher in Asia (5.8%; I^2=97.6%) and South America (5.6%; I^2=2.5%) compared with European countries (0.6%; I2=85.0%). Higher MRSA prevalence was reported by studies conducted in the community (5.7%; I^2=96.7%) and healthcare centres (6.4%; I^2=98.0%) when compared with children's institutions (ie, nurseries, kindergartens, daycare centres and preschools) (1.5%; I^2=89.9%). Although these significant factors can partially explain the heterogeneity, there is still relatively high heterogeneity within different subgroups.

Significant risk factors

Seven of the 35 included observational studies reported the significant risk factors/predictors of asymptomatic MRSA colonisation for the target population. Specifically, previous antibiotic intake history and having an MRSA-colonised mother were significantly associated with asymptomatic MRSA colonisation in young children. Other significant risk factors are reported in table 1.

Antibiotic resistance characterisation

Antibiotic resistance characteristics of MRSA isolates were extracted from a total of 14 studies out of 35 studies (detailed in online supplemental appendix VII). High pooled resistance rates (ie, higher than 60%) were observed for antibiotics, such as ampicillin (93.3%; I^2=44.7%) and erythromycin (63.0%; I^2=89.6%), while the resistance rates to some important antibiotics remained low, such as rifampin (0.3%; I^2=0.0%) and fusidic acid (0.0%; I^2=0.0). Only one isolate found by Sedighi et al[40] was resistant to vancomycin.

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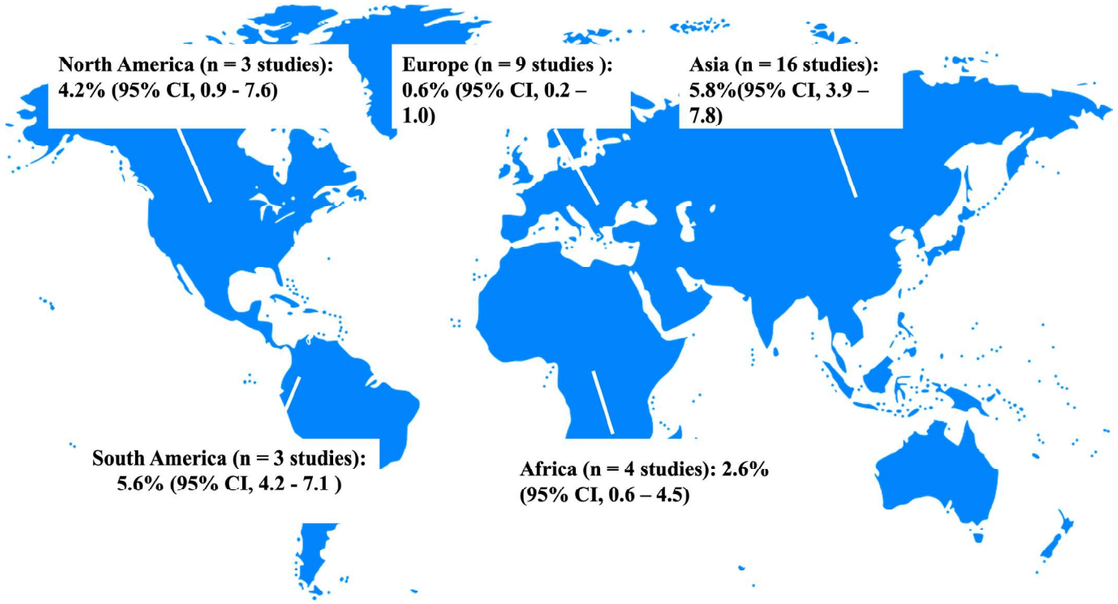

Figure 4 Prevalence of asymptomatic colonisation of MRSA in the upper respiratory tracts of young children in five continents. MRSA, methicillin-resistant *Staphylococcus aureus*.

Molecular genetic characterisation

Only a few studies characterised the molecular genetic characteristics of MRSA isolates from their target population. Among 13 studies that tested for the mecA gene, all isolates were positive (539/539).[20 21 23 25 27 28 32 33 36 39 43 46] Yet, the pooled positive rate of the Panton-Valentine leucocidin (PVL) gene was 14.7% (95% CI 4.3 to 25.0) with high heterogeneity (I^2=89.1%) among 493 MRSA isolates from 13 studies.[16 17 20–22 25 28 33 35 36 43 46 47] SCCmec type IV (319/487) was the predominant SCCmec type, followed by type VT (84/487), type I (20/487) and type V (14/487).[16 21 22 25 28 32 33 35 36 43 46 47] Tsai et al[46] found that the PVL gene was predominantly associated with SCCmec type VT or IV isolates. Different MRSA variations were reported in different studies. In particular, ST59 was the most commonly observed isolate in Taiwan, and sporadic MRSA isolates (ie, single locus variants of ST9) belonging to livestock-associated MRSA (LA-MRSA) clones were found in two children.[46] Scn-negative MRSA (a putative marker for LA-MRSA) was observed in a child from a family involved in industrial hog farming and processing[23] and one ST398-MRSA-V was detected in a child without exposure to livestock.[22]

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis on the global prevalence and epidemiology of asymptomatic MRSA colonisation in young children. This study estimated the global asymptomatic MRSA colonisation in children using 35 studies published between 2010 and 2021. The pooled prevalence of asymptomatic *S. aureus* and MRSA colonisation was 25.1% (95% CI 21.4 to 28.8) and 3.4% (95% CI 2.8 to 4.1) in young children, respectively. Compared with pooled MRSA colonisation and infection prevalence of 2.8% (95% CI 1.6 to 4.0) among children (0–5 years old) in a systematic review using data published between 2000 and 2010,[48] the overall asymptomatic colonisation prevalence increased among young children in the last 10–15 years. Furthermore, the prevalence was higher in young children than in healthy people, with a prevalence of 5.9% (95% CI 2.3 to 79.6) and 0.8% (95% CI 0.0 to 17.5) for *S. aureus* and MRSA colonisation, respectively, for the latter cohort.[49] It is also supported by a meta-analysis conducted for the Asia-Pacific region reporting higher CA-MRSA prevalence in young children under 6 years old with less mature immune systems than older children or adults.[50] This is a warning finding as a study conducted by von Eiff et al[51] presented evidence to support that *S. aureus* in the nasal mucosa could be an endogenous origin for bacteraemia. Compared with non-carriers, both low (Ct>24 cycles) burden and high burden (Ct≤24 cycles) of nasal colonisation was associated with subsequent MRSA infection.[52]

Considerable heterogeneity in estimates of prevalence is mainly related to the continent, age of subjects and screening setting. MRSA became more prevalent in some Asian and Latin American countries.[53 54] A much higher MRSA prevalence in Asia (5.8%) and in South America (5.6%) was reported compared with Europe (0.6%). Studies conducted in mainland China and Taiwan[34 44 46] reported a higher prevalence of asymptomatic MRSA colonisation than others, while studies conducted in Hungary reported a lower prevalence.[31,32] It is important to note that a proportion of children recruited in a study conducted in the US was from households of industrial hog operation workers, which has been considered to be a risk factor for MRSA colonisation.[23] Therefore, the prevalence of MRSA colonisation reported in this study was much higher than the prevalence reported in other publications from the North America.[27 35] Furthermore, a higher prevalence of asymptomatic MRSA colonisation was observed among young children recruited from communities and healthcare centres (without infections caused by *S. aureus*) than in children's institutions, although this classification may partially overlap due to the difficulty in clearly separating them based on the description in the original research publications. Nonetheless, children attending child care centres are usually with a higher risk to of MRSA infection[55] and can be a potential reservoir for emerging MRSA genotypes.[56] More importantly, a previous study suggested that CA-MRSA infections were more likely to occur in children under 3 years old than in older children.[57] Similarly, in this study, the prevalence of asymptomatic

MRSA colonisation in newborns (within the first month) was significantly higher than in the older children, which is consistent with a meta-analysis that suggested the prevalence of MRSA colonisation in newborns (within 28 days) was significantly higher than in young children (within 5 years old), regardless of the subject's health status of subjects at the sampling time.[48] This finding highlights the importance of monitoring the prevalence and persistence of asymptomatic MRSA colonisation in children, particularly in the younger age group. However, it should be noted that the subgroup analysis for age in our study was largely influenced by a longitudinal study conducted in Keelung City, Taiwan.[44] In this cohort, 29.4% of the newborns were colonised by MRSA at the age of 1 month. Interestingly, the colonisation rate of both *S. aureus* and MRSA gradually decreased in the first year of their life, which may be due to the pneumococcal competition in the nasopharyngeal space.[44]

Genetically, SCCmec type IV or VT remained the predominant SCCmec type and was mainly associated with the presence of the PVL gene,[46] consistent with the genetic pattern observed 10–15 years ago.[48] The predominant SCCmec type IV, VT and V are associated with CA-MRSA, while type I is associated with hospital-acquired MRSA (HA-MRSA).[58 59] In addition, LA-MRSA was reported in young children, though the prevalence was low.[22 23 46] Therefore, it suggests that either CA-MRSA, HA-MRSA or LA-MRSA may be present in the upper respiratory tracts of young children without respiratory infection symptoms.

There are several limitations in this study. First, the languages of the included publications were restricted to English and Chinese, which may introduce bias to the prevalence estimates.

Second, the substantial heterogeneity and publication bias across included studies may affect the estimation precision. However, since it is a small meta-analysis with 35 studies, it should be noted that the I^2 is known to be inevitably less precise in practice.[60] In addition, a large proportion of isolates (330 isolates) in our study was contributed by Tsai and colleagues,[46] which may cause systematic errors in estimating the resistance rate to some antibiotics and genetic characterisation. Third, the prevalence of MRSA colonisation in the respiratory tract may be underestimated in this meta-analysis because all included studies used culture-based methods with lower sensitivity instead of the PCR method to detect *S. aureus*.[61] Finally, considering that MRSA prevalence varies widely across different regions, and a higher number of studies may be conducted in regions with higher reported infection cases, more cross-regional routine surveillance studies are expected.

CONCLUSIONS

In conclusion, our study provides evidence from an important aspect for establishing MRSA infection control among young children. The prevalence of asymptomatic MRSA colonisation was associated with geography, screening setting, children with younger age, previous antibiotic intake history. The increasing colonisation rate and considerable heterogeneity in prevalence estimates highlighted the need for more cross-regional active surveillance on asymptomatic colonisation in early childhood care to avoid a wider spread of MRSA and subsequent infections.

Table 1 Reported significant risk factors/predictors of the asymptomatic colonisation of MRSA in the upper respiratory tract in young children

Study	Study design	Setting (country)	Age	Statistical analysis	Risk factors/predictors	Relevant statistical data
Fan *et al*[20]	Cross-sectional	Kindergartens (China)	2–7 years	Univariate	► Attending day kindergartens compared with full day kindergartens; ► Antibiotic intake within 6 months.	► Pearson x^2; p=0.027 ► Data not shown
Jimenez-Truque[27]	Prospective	Obstetrics Clinic of Hospitals (America)	At birth (within 2 hours)	Univariate	► Have an Africa American mother; ► Have been born vaginally.	► Pearson x^2; p<0.001 ► Pearson x^2; p=0.018
Biber *et al*[13]	Cross-sectional	Neighbourhoods and village (Gaza Strip)	0–5.5 years	Multivariate	► Having a MRSA carrier parent.	► OR=25.5; p=0.0004
Braga *et al*[15]	Cross-sectional	Public daycare centres (Brazil)	3 months to 6 years	Bivariate	► Use ß-Lactam antibiotic in the previous 30 days; ► Attend daycare centres located in aglomerado subnormal (AGSN) census tract.	► Pearson x^2; p=0.003 ► Pearson x^2; p<0.001
Hatcher *et al*[23]	Cross-sectional	Industrial hog operations (IHOs) families and non-IHOs families (America)	0–7 years	Bivariate	► Live with IHO workers; ► Occupational activities of IHO workers.	► Adjusted risk ratio=2.37 (95% CI, 1.14 to 4.92) ► Crude risk ratio[a]
Heigl *et al*[24]	Cross-sectional	Hospitals (Germany)	At birth and 3 days after birth	Univariate	► Have a MRSA colonised mother.	► Risk ratio=216.3 (95% CI, 69.59 to 672.53).
Dayie *et al*[17]	Cross-sectional	Nurseries and kindergartens (Ghana)	0–5 years	Univariate	► Age group (the prevalence of age between 37 and 48 months was the highest).	► Pearson x^2; p=0.003

[a] take PPE (personal protective equipment) home: 12.07 (95% CI, 3.78 to 38.60); use disinfectant: 6.25 (95% CI, 1.95 to 20.01); work with nursery pigs: 2.23 (95% CI, 1.12 to 4.45); handle dead pigs: 3.21 (95% CI, 1.01 to 10.19).
MRSA, methicillin-resistant *Staphylococcus aureus*.

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ARTIGO ORIGINAL

Resultados da função pulmonar após tratamento da tuberculose em crianças: uma revisão sistemática e meta-análise

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RESUMO

Contexto Apesar de a tuberculose (TB) ser uma doença curável, as orientações atuais não têm em consideração os resultados a longo prazo da doença pulmonar pós-tuberculose - uma causa de morbilidade global apesar da conclusão bem-sucedida de um tratamento eficaz. A nossa revisão sistemática teve como objetivo sintetizar a evidência disponível sobre os resultados da função pulmonar da tuberculose pulmonar (TBP) infantil.

Métodos Foram pesquisadas as bases de dados PubMed, ISI Web of Science, Cochrane Library e ProQuest para estudos apenas em inglês, sem restrição de tempo (data da última pesquisa: 22 de março de 2023). Os critérios de inclusão consistiram em (1) doentes com TB com envolvimento pulmonar com idade ≤18 anos, (2) testes de função pulmonar (TFP) realizados em doentes após a conclusão do tratamento e (3) estudos observacionais, incluindo estudos de coorte e transversais. Seguimos as recomendações da Cochrane Collaboration e dos Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Resultados De 8040 registos, foram incluídos 5 estudos (envolvendo n=567 crianças), com medidas espirométricas de 4 estudos incluídas nas meta-análises. Os tamanhos dos efeitos da TB infantil no volume expiratório forçado no primeiro segundo e nos valores z da capacidade vital forçada foram estimados em -1,53 (IC 95% -2,65, -0,41; p=0,007) e -1,93 (IC 95% -3,35, -0,50; p=0,008), respetivamente.

Discussão O número reduzido de estudos incluídos reflete esta área pouco investigada, em comparação com o fardo global da TB. No entanto, uma vez que a TBP infantil tem impacto na função pulmonar futura, os TFP (como a espirometria) devem ser considerados um teste de rotina na avaliação da saúde pulmonar a longo prazo das crianças após a conclusão do tratamento da TB.

Número de registo PROSPERO CRD42021250172.

Key messages

What is the key question?

- ▶Tuberculosis (TB) is a treatable disease, but despite resolution of the infection, lung function deficits associated with post-tuberculosis lung disease (PTLD) can persist.
- ▶ While this is well appreciated in adults, the extent and severity of PTLD in children are not well characterised.
- ▶This area of work is important because of the potential long-term impacts of PTLD on children's lung health and development.

What is the bottom line?

- ▶Our meta-analyses showed that childhood TB causes significant decline in at least two spirometry parameters despite high levels of between-study heterogeneity.
- ▶ The effect sizes of childhood TB on forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) z-scores were clinically significant.
- ▶ While direct comparison with published adult TB studies was not possible, this study suggests that childhood TB results in PTLD.

Why read on?

- ▶This study supports incorporation of routine pulmonary function tests into the follow-up of children with history of TB, allowing for early detection and management of PTLD.

INTRODUCTION

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis*. Inhalation of the bacterium into the airways can result in TB infection. Pulmonary disease is established when the host's innate immune response is unable to eliminate the bacterium.[1] In 2021, an estimated 10.6 million people fell ill from TB globally, and children under 15 years old accounted for 11% of this burden.[2] Childhood TB causes a spectrum of clinical presentations, most commonly pulmonary disease. Irrespective of organ involvement, obtaining bacteriological confirmation for infants and young children still proves challenging. Age is the key determinant of disease progression, with risk of progression to pulmonary tuberculosis (PTB) about 30%–40% when primary infection occurs in infants under a year old.[3] While improving the diagnosis and management of childhood TB is important,[4] children with prior PTB can experience detrimental changes irrespective of successful completion of treatment.[5] There is a significant knowledge gap in the occurrence and severity of post-tuberculosis lung disease (PTLD) in children.[6] Adult PTLD is better described, including post-TB bronchiectasis[7] and lung function changes.[8] One study reported decline in mean forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) z-scores by −1.07 and −0.91 on treatment completion, and −0.91 and −0.64, respectively, 3 years post-treatment.[9]

Specific data on childhood PTLD are required as early-life lung injuries from respiratory infections and pneumonia cause deficits during children's peak lung growth and development.[10] It is possible that childhood PTB is more detrimental to future lung function, compared with acquiring PTB as TB-naïve adults. A recent review recommended the evaluation of PTLD using objective tests for early detection of post-TB pulmonary changes ir-

Artigo original

respective of symptoms.[11] These could promote initiation of treatments to prevent irreversible lung function decline, reduce healthcare costs, and alleviate burden to patients, their families and healthcare systems.

Given the absence of a systematic review evaluating the effects of childhood TB on pulmonary function test (PFT) outcomes, we undertook this review and meta-analysis aiming to synthesise available evidence regarding the effects of childhood PTB on future lung function.

METHODS

This systematic review was registered in PROSPERO with identification number CRD42021250172. Deviations from the registered protocol were (1) redefining the primary outcome as spirometry measurements and the secondary outcome as non-spirometry measures of lung function; and (2) reduced number of searched databases due to record duplication. Study findings were reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines and checklist.[12]

Literature search

Eligible studies were searched from PubMed, Cochrane Library and ISI Web of Science databases up to 22 March 2023 (online supplemental appendix 1). Grey literature searches were performed on ProQuest database, followed by manual citation searching of included studies. No publications were excluded based on publication date.

Eligibility criteria

Included studies fulfilled the following inclusion criteria: (1) patients with TB with pulmonary involvement at age ≤18 years; (2) PFTs performed on patients after treatment completion; and (3) observational studies, including cohort and cross-sectional studies. The exclusion criteria were (1) mixed-population studies which did not report the ≤18 years subgroup separately, (2) TB studies without pulmonary involvement, (3) evidence of non-standard anti-TB treatment regimens, (4) did not perform PFTs post-treatment or (5) reviews and case studies.

Studies from all countries and settings were included. Studies were included regardless of bacteriological confirmation, unreported treatment regimens or timing of PFTs. Studies with other concurrent disease as primary domain were included providing that PFT measures were sufficiently reported for inclusion in the analysis.

Outcomes

The primary outcomes were spirometry measures. The secondary outcomes were measurements from non-spirometry PFTs. There were no limits to the timing of PFTs after completion of TB treatment.

Data extraction and quality assessment

Screening and eligibility assessment was performed by two reviewers independently (YLL and AFT). The references of eligible studies were assessed to ensure inclusion of relevant studies. No automation tools were used throughout the review process. For eligible studies, data extraction was performed according to a standardised collection form (online supplemental appendix 2). Using the Newcastle-Ottawa Scale, both reviewers independently assessed the studies' risk of bias and certainty assessments, with consensus achieved through discussion.[13]

Statistical analysis

All statistical analyses were done using R for Windows (V.4.2.2).[14] The median and IQR were normalised to give mean and SD, where the distance between Q1 to median was equal to median to Q3.[15] Spirometry results presented as percentage of predicted values were converted to z-scores using the 'rspiro' package,[16] based on the Global Lung Function Initiative (GLI)-2012 equation,[17] accounting for North East Asian ethnicity, mean age of 11.9 years, a male to female ratio of 53.5:46.5 and a median height for age based on the 2017 Korean National Growth Charts.[18] Studies which reported primary outcomes were included in the meta-analyses, and effect sizes were calculated using Hedges' g and presented with 95% CI.[19] Secondary outcomes not included in the meta-analyses were presented separately.

We used random-effects models (DerSimonian-Laird method) to estimate overall effect due to variable data with significant heterogeneity. Between-study heterogeneity was assessed using the I^2 statistic, with values >75% representing considerable heterogeneity. Meta-analyses were performed using the 'metafor' package.[20] Sensitivity analysis was not performed as substantial interstudy differences rendered statistical approaches meaningless.

RESULTS

Search results

The screening process is detailed in figure 1. After removing duplicates, 8040 records were screened, from which we reviewed 34 full-text articles and finally included 5 studies.[21–25] The characteristics of the excluded studies are summarised in online supplemental appendix 3.

Characteristics of included studies

The included studies were studies conducted in urban or periurban settings of TB-endemic countries of Africa, except for one retrospective review study in South Korea, a country with upper-moderate TB incidence.[22] A total of 567 children with history of PTB were included; the median number of children in the studies was 68 (range: 42–305).[21–25] Key characteristics are reported in table 1, and details of quality scores are shown in online supplemental appendix 4. One study performed non-spirometry PFTs after early-life TB[25] and was thus excluded from the meta-analyses. Granular details of the studies included in the meta-analyses are provided in online supplemental appendix 5.

Diagnosis and treatment of PTB

Bacteriological confirmation of TB varied between studies, ranging from 13.7%[25] to 58.5%.[22] GeneXpert MTB/RIF was used to rule out active infection pre-spirometry. [21 26] Only one study reported treatment regimen for drug-susceptible TB according to national guidelines, modified for drug resistance[25]; other studies[21–24] did not report treatment regimen details.

Pulmonary function tests

The time between treatment completion to PFTs ranged between 6 and 24 months in the three most recent studies[23–25]; two earlier studies[21 22] did not specify this duration. Three studies[21–23] reported performing spirometry according to the American Thoracic Society/European Respiratory Society 2005 standards,[27] and one[24] according to the 2019 update.[28] Three studies[21 23 24] performed bronchodilator responsiveness testing.

For the effects of childhood TB on FEV_1 and FVC z-scores, meta-analyses were possible and these are presented in forest plots, with pooled effect size estimates of −1.53 (95% CI −2.65, −0.41; p=0.007; figure 2) and −1.93 (95% CI −3.35, −0.50; p=0.008; figure 3).

Meta-analysis was not possible for FEV_1:FVC ratios presented in the included studies, thus summarised in table 2 instead. Only one study performed non-spirometry PFTs. Association coefficients between childhood PTB occurring between 1 and 4 years of age with measurements taken at 5 years are reported and presented in online supplemental appendix 6.[25] Only one study reported lung function patterns directly attributed to PTB. Spirometry taken at 19.2 (IQR: 10.2–44.4) months after TB diagnosis showed 61.5% (32/52) with normal lung function, 36.5% (19/52) with restriction and 2% (1/52) with obstructive patterns at a median age of 8.9 (IQR: 7.2–11.2) years.[24]

Heterogeneity, sensitivity and bias

Due to the small number of studies, sensitivity analysis was not performed. Significant between-study heterogeneity was observed

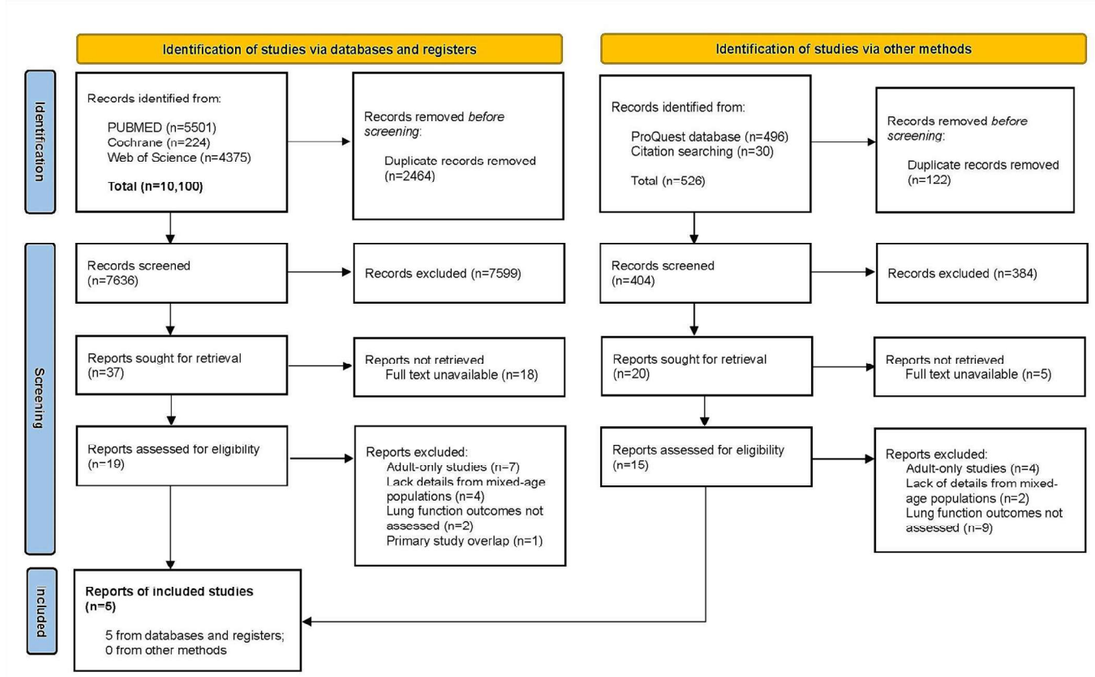

Figure 1 PRISMA diagram showing identification, screening and inclusion of studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

in the meta-analyses for FEV_1 and FVC effect sizes at I^2=89.11% (p<0.0001) and I^2=91.63% (p<0.0001), respectively, as indicated by the blue diamonds in figure 2 and figure 3. The study[22] which reported PTB–bronchiectasis overlap had the largest effect size on both FEV_1 and FVC z-scores. The exclusion of this study[22] from the meta-analysis for FEV_1 led to a significant reduction in heterogeneity, as shown by the red diamond in figure 2, but not observed in the meta-analysis for FVC.

Publication bias was judged as unlikely as the included studies were observational, funded by research grants and unlikely to be influenced by industry-based sponsorship or agenda. It was notable that three included studies reported primarily on non-TB diseases, thus less likely to be affected by reporting bias in terms of PTB-related outcomes, at the cost of being less comprehensive in reporting PTB-related details.[21–23] One included study had significant information bias as summary statistics were not reported numerically, necessitating pixel counting of error bars from interval plots to approximate the data dispersion within the PTB subgroup.[22]

DISCUSSION

Interpretation of results

The small number of included studies highlights under-representation of childhood TB globally.[2] The overall direction of effects of PTB on lung function was negative, that is, reduced lung function in both meta-analyses of FEV_1 and FVC. These findings align with our current understanding of PTLD in adults,[29] lending further support to the validity of our approach. While pooled effect sizes appear to be significant, high I^2 values indicate substantial between-study heterogeneity, which is a key limitation in our study. This suggests a research gap in quantifying the impact of PTB during childhood on lung function outcomes, particularly in high-prevalence settings.

Of the included studies, three had primary diseases[21–23] that were not PTB, which were reasonable to include as HIV coinfection is a significant comorbidity[30] and bronchiectasis is a well-established sequela of PTB.[6] One study[24] evaluated health-related quality of life post-PTB, suggestive of recent paradigm shifts to better evaluate PTLD. As only two studies reported spirometry performed at >24 months[23] and >6 months[24] after treatment completion, the actual effect of spirometry timing was indeterminate due to variability of the included studies. A prospective cohort of adult TB survivors did show greater deterioration in FEV_1 and FVC values 3 years after treatment completion[9] compared with the first year post-treatment.[29]

Due to a low quality score, contextual interpretation for one included study[22] is presented here. As the GLI-2012 equation[17] for North East Asian ethnicity was developed using only subjects aged ≥16 years, the spirometry z-scores for young children in this study[22] were calculated using extrapolation, which may have inadvertently inflated the effect sizes. This inference was partially supported by a validation study[31] which found that South Korean females aged 7–8 years have mean FEV_1 and FVC z-scores lower than the GLI-2012 predictions by −0.23 (95% CI −0.31, −0.15) and −0.26 (95% CI −0.36, −0.16), respectively, suggesting the actual lung function for this subgroup is slightly below established baseline. A secondary analysis which excluded this outlier study[22] from the meta-analyses yielded an alternative random-effects model for FEV_1 based on three studies with reduced statistical heterogeneity (red diamond; figure 2). As pooled effect sizes regardless of exclusion remained below −0.8, the overall interpretation was that childhood TB exerts a large effect[32] on FEV_1. Removal of this study[22] did not appreciably change the pooled effect size estimate nor the I^2 statistic for FVC (not shown). It is noteworthy that one study[23] reported more significant HIV-associated decline in FVC than FEV_1; the combinatory effect of PTB within an all-HIV cohort gave a greater change in FVC relative to baseline and subsequently a larger standardised effect size as compared with FEV_1. This was partly supported by another study[10] which found early childhood respiratory infections had a marginally greater effect on FVC than FEV_1, raising plausibility that HIV coinfection is a clinical contributor to heterogeneity observed in figure 3.

Table 1 Included studies and their characteristics

Study	Country	Date range of data collection	Study design	Participants with PTB/ total study participants	Bacteriological confirmation rate for PTB cases (%)	Non-bacteriological diagnosis of PTB	Primary disease domain of included study	HIV status of children with PTB (%)	Age at of PFT performed on participants with PTB, mean (SD) or median (IQR)	Time between TB treatment to PFT	Reported lung function measures	Quality score
Sovershaeva *et al*[21]	Zimbabwe	2017–2018	Cross-sectional	57/319	Unspecified	Participant questionnaires	HIV	100	15 (12–18)	Unspecified	FEV_1 (z-score), as median	5/8
Lee *et al*[22]	South Korea	2000–2018	Retrospective cross-sectional	42/341	59.5 (25/42)	Extracted hospital records; Mantoux skin test	Bronchiectasis	Unspecified	11.9 (5.6)	Unspecified	FEV_1 (% predicted) and FVC (% predicted), as means	4/8
Githinji *et al*[23]	South Africa	2013–2017	Cohort study	305/609	Unspecified	Extracted hospital records and validated study questionnaires	HIV	100	12 (1.6)	≥24 months	FEV_1 (z-score), FVC (z-score) and FEV_1:FVC (z-score), as association coefficients	7/9
Nkereuwem *et al*[24]	Gambia	2020–2021	Cross-sectional	68/159	35.3 (24/68)	At least two from signs of TB, suggestive CXR, positive response to TB treatment or prior exposure to TB	PTB	13.2 (9/68)	8.9 (7.2–11.2)	Median: 19.2 (IQR: 10.2–44.4) months	FEV_1 (z-score), FVC (z-score) and FEV_1:FVC (z-score), as means	7/8
Martinez *et al*[25]	South Africa	2012–2020	Prospective birth cohort	95/1068	13.7 (13/95)	At least two from signs and symptoms of TB, suggestive CXR or prior exposure to TB	PTB	0	5	≥6 months, except in cases of drug resistance	Functional residual capacity (L), lung clearance index (n turnovers), tidal volume (mL), respiratory rate (breaths/min), minute ventilation (L/min), t_{PTEF}/t_E (%), t_I/t_{TOT} (%), compliance ($mL.hPa^{-1}$) and resistance ($hPa.sL^{-1}$), as association coefficients	9/9

FEV_1, forced expiratory volume in the first second; CXR, chest X-ray; FVC, forced vital capacity; PFT, pulmonary function test; PTB, pulmonary tuberculosis; TB, tuberculosis; t_I/t_{TOT}, inspiratory time of one breath (in seconds); t_{PTEF}/t_E, time to peak tidal expiratory flow over total expiratory time.

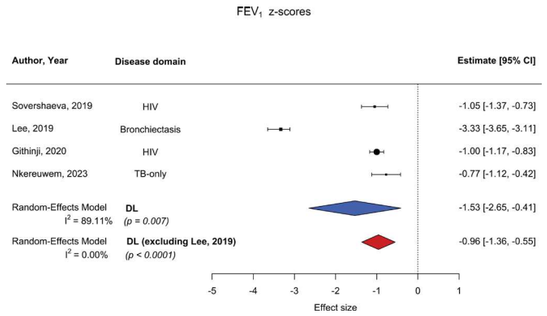

Figure 2 Forest plot of effect sizes of childhood pulmonary tuberculosis on FEV_1 z-scores. DL, DerSimonian and Laird method; FEV_1, forced expiratory volume in the first second; TB, tuberculosis.

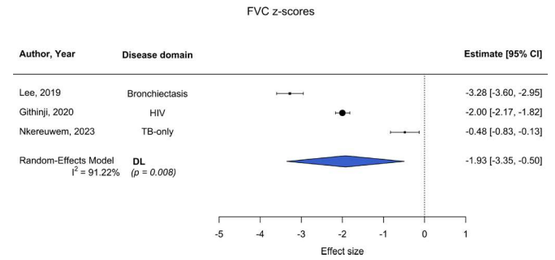

Figure 3 Forest plot of effect sizes of childhood pulmonary tuberculosis on FVC z-scores. DL, DerSimonian and Laird method; FVC, forced vital capacity; TB, tuberculosis.

Limitations of evidence and review process

The included evidence had limitations inherent to the population, nature of disease and outcome measures. The WHO classifies childhood TB as diagnosed in children <15 years old, leading to bias in age stratification at study design level.[2] Adolescents aged ≥15 years are classified as adults, inadvertently excluding evidence encompassing full age range of childhood. Bacteriological confirmation of TB was relatively low (range: 13.7%–59.5%); thus, misclassification bias among children with clinically diagnosed TB was possible.[33] Numerical SD values were not reported in one study[22], requiring manual pixel-counting based on published figures, measurement errors arising from this step may be propagated when Hedges' g was calculated.

One study[23] reported z-score changes as association coefficients, thus necessitating Fisher's z-transformation,[34] resulting in CIs that were much smaller than other studies[21 22 24] included in the meta-analyses. Thus, pooled effect sizes should be interpreted with awareness of our approach used.

Clinical and policy implications

To the best of our knowledge, this is the first meta-analysis to investigate the effects of childhood PTB on lung function decline. Our findings suggest that childhood PTB is associated with overall decreases in subsequent FEV_1 and FVC z-scores. Concurrent bronchiectasis exerted the greatest additive negative impact on spirometry parameters compared with HIV coinfection or TB on its own.[22] Childhood TB and resultant PTLD remain understudied within paediatric populations despite clear association with lung function decline, further compounded by underdiagnosis and subsequent failure to treat.[2 6]

WHO-defined outcomes of TB treatment include cured or treatment completed positive outcomes, and negative outcomes of lost to follow-up, treatment failure or death.[35] These outcome indicators are based primarily on bacteriological clearance and treatment compliance, with post-TB sequelae and residual respiratory impairment unaccounted for. The most recent roadmap for ending TB in children and adolescents does not address the fact that post-TB disabilities and PTLD do occur beyond completion of treatment.[36]

In the first consensus-based set of clinical standards for PTLD,[37] the foremost standard recommends clinical, functional and subjective evaluation of every patient completing TB treatment for PTLD, with considerations for paediatric care, including selection of age-appropriate PFTs and quality-of-life questionnaires. The second and third standards called for evaluating patients with PTLD for pulmonary rehabilitation (PR) and the organisation of PR programmes with health settings and individual patients' needs in mind. While not routinely done for children and thus far unreported for childhood PTB, individualised PR programmes have been attempted for paediatric asthma[38] and could be adjusted to younger patients in high-TB settings.

Objective lung function measurements allow for prompt initiation of PR[37] or other adjunctive therapies[39] to prevent late-life onset of respiratory diseases such as bronchiectasis, asthma or chronic obstructive pulmonary disease. As performing spirometry on young children can be challenging, non-spirometry PFTs should be considered for children below certain ages and others on a case-by-case basis. At least one study has explored oscillometry for children above 2 years, alongside spirometry for those above 4 years of age.[40] Subsequent findings may address the evidence gap for performing scheduled PFTs as part of national TB programmes or routine post-TB pulmonary health surveillance,[11] especially in low-income to middle-income countries with significant disease burden. Our findings suggest that spirometry or other PFTs should be performed as routine follow-up of children beyond TB treatment completion to monitor their lung function and diagnose any impairments promptly. Lung health monitoring enables appropriate and timely interventions to reduce the frequency and severity of PTLD beyond treatment completion.

Contributors YLL collected and analysed the data, and wrote and revised the manuscript; YLL accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish. YLL is guarantor. AFT collected and analysed the data, and reviewed the manuscript. SY critically reviewed the data analysis and interpretation, and reviewed the manuscript. TWY conceptualised and designed the study, and provided supervision. AC conceptualised the study, critically reviewed the manuscript and provided supervision. CL reviewed the initial analysis, critically reviewed the manuscript and provided supervision.
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Table 2 Summary of studies reporting FEV_1:FVC ratios in any manner

Study	Disease domain	Metrics	Mean	Association coefficient	P value
Lee *et al*[22]	Bronchiectasis and TB	% predicted	Plotted*	n.a.	n.a.
Githinji *et al*[23]	HIV and PTB	z-scores	n.a.	−0.01†	0.904
Nkereuwem *et al*[24]	PTB only	z-scores	−0.54 (0.91)	n.a.	0.001

*Mean FEV_1:FVC ratio was presented as an interval plot, but the value provided was incorrectly labelled.
†95% CI unreported.
FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; n.a., not available; PTB, pulmonary tuberculosis; TB, tuberculosis.

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ARTIGO ORIGINAL

A ecografia no ponto de assistência como ferramenta de diagnóstico na avaliação respiratória em doentes pediátricos acordados: um estudo comparativo

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RESUMO

Contexto Tipicamente, a radiografia do tórax (RXT) tem sido a investigação principal em crianças com suspeita de patologia respiratória. Os recentes avanços na ecografia pulmonar no ponto de assistência (POCUS) demonstraram o seu potencial para ser comparável, se não superior, à RXT. O objetivo deste estudo foi comparar a RXT com a POCUS pulmonar em crianças com doença respiratória num hospital universitário pediátrico.

Métodos Todas as crianças com menos de 18 anos de idade que se apresentaram no Southampton Children's Hospital e que necessitaram de uma RXT por razões clínicas também foram submetidas a uma POCUS pulmonar. A RXT foi relatada por um radiologista pediátrico consultor e a POCUS pulmonar foi analisada retrospetivamente por um clínico de POCUS ocultado, apenas com as informações clínicas fornecidas no pedido de RXT. Foram efetuadas comparações entre os achados da RXT e da POCUS pulmonar.

Resultados Foram incluídos no estudo 100 pares de POCUS pulmonar e RXT. 30% das POCUS pulmonares estavam normais e 97% destas apresentavam uma RXT normal. 70% dos casos apresentaram anomalias na POCUS, com 96% dos casos de POCUS a identificarem patologia pulmonar comparativa. Por conseguinte, a POCUS pulmonar apresentou uma sensibilidade de 98,51% e uma especificidade de 87,9% com uma exatidão de diagnóstico de 95% quando comparada com o relatório da RXT.

Conclusões A POCUS pulmonar tem uma excelente precisão de diagnóstico. O diagnóstico de pulmão normal na POCUS, quando efetuado por um profissional treinado, pode reduzir de forma fiável a necessidade de uma RXT, reduzindo assim a utilização de RXT e a exposição à radiação em crianças. Assim, uma POCUS pulmonar anormal pode fornecer o diagnóstico ou conduzir a uma RXT com a expetativa de achados clinicamente relevantes.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ▶Lung point-of-care ultrasound is a safe and accurate tool to diagnose respiratory pathology.
- ▶ Lung point-of-care ultrasound is a well-used modality in adult specialties.
- ▶ Lung point-of-care ultrasound is regularly used in paediatric intensive care units and has a growing interest in neonatal and general paediatrics.

WHAT THIS STUDY ADDS

- ▶A normal lung point-of-care ultrasound is reliably associated with a normal chest X-ray.
- ▶ An abnormal lung point-of-care ultrasound is reliably associated with an abnormal chest X-ray.
- ▶ Lung point-of-care ultrasound is highly sensitive and specific at making a respiratory diagnosis when compared with the chest X-ray.
- ▶ Lung point-of-care ultrasound can be reliably performed in a general paediatric cohort by trained medical and nursing staff.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ▶Provides data to support the increase in training on point-of-care ultrasound to paediatric staff.
- ▶ Provides data to support the reduction in the need for unnecessary chest X-ray use if the lung ultrasound is normal.

INTRODUCTION

Over the past 10 years, the use of lung point-of-care ultrasound (POCUS) by clinicians outside of the field of radiology has significantly increased in daily clinical practice.[1–3] The use of POCUS provides a rapid, dynamic and easily repeatable investigation which can be performed at the bedside with simple and affordable equipment. Adult critical care and emergency medicine have been leaders in this development and several studies have focused on the sensitivity and specificity of POCUS compared with the current gold standard of chest X-ray (CXR) and chest CT in adult patients.[4]

The use of POCUS for clinical decision making in the paediatric population should be considered easier than in the adult population, due to lower amounts of subcutaneous fat, improved acoustic windows due to partially ossified chest wall structuresand a reduced depth for ultrasound penetrance.[5] However, despite data suggesting the effectiveness of POCUS in children,[6–8] its use is still generally confined to paediatric intensive care settings and occasional use in paediatric emergency departments.[7 9] The reasons for this are related to the lack of experience of senior paediatricians in the use of POCUS as a bedside diagnostic tool and the paucity of paediatric-specific training packages for developing the required competencies in image attainment and interpretation.[10 11] Despite these limitations, a number of paediatric studies have shown that POCUS can complement traditional imaging modalities for the diagnosis and

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continued monitoring of paediatric lung pathologies.[1 6–8] There are several logistical challenges that are recognised with the use of traditional CXR for diagnostic purposes, including transfer to a radiology setting, with the associated infection control risks, the need for accompanying staff and the potential safety risks of transferring clinically unstable or injured children. With the additional disadvantage of CXR exposing patients to ionising radiation, it can be difficult to justify repeat investigations to monitor pathology. In view of these facts, POCUS is now thought of as an essential skill by many paediatric trainees.[12]

A recent review article by Musolino et al[4] examined the use of POCUS over the last 10 years and concluded that it should be considered the first-choice tool for the diagnosis and follow-up of paediatric lung diseases. Most papers in this review focused on the use of POCUS in children in intensive care settings, however, investigation of paediatric lung disease is most frequently performed on conscious, active, non-compliant children.

OBJECTIVES

Our study aimed to determine if lung POCUS in a ward-based setting is comparable to the currently used role of CXR in identifying respiratory pathology in a population of awake general paediatric patients, therefore enabling this modality to be used as a screening tool to reduce the number of CXR performed. The secondary aims were to identify:

- if it was possible to obtain reliable, consistent POCUS images in a population of awake children of varying ages;
- if the findings of POCUS were consistent with radiologist reporting of comparable CXR;
- if POCUS was more sensitive and specific at identifying normal or abnormal lungs when compared with a ward-based doctor interpretation of acute CXR.

This paper does not seek to detail the diagnostic findings, which can be achieved by POCUS in clinical practice as this is well described in other studies.[1 13 14]

METHODS

Setting

This study was performed by the paediatric high dependency team (two consultants and two registrars) and the paediatric outreach nursing team (seven advanced nurse practitioners) at Southampton Children's Hospital, UK. All members of the investigative team had been trained using combined materials from the Focused Ultrasound in Intensive Care (FUSIC)[15] training package from the Intensive Care Society and the Children's Acute Ultrasound (CACTUS)[16] course from the Paediatric Intensive Care Society. Prior to the study taking place, all members of the team had been assessed by a FUSIC/CACTUS supervisor for their ability to obtain interpretable POCUS images.

Data collection

The study aimed to recruit a convenience sample of 100 patients. Data collection was conducted over an 8-month period between January and August 2021. Inclusion criteria were any child (aged 0–18 years) requiring a CXR for any clinical indication within the Children's Hospital. Exclusion criteria were any child on the paediatric or neonatal intensive care unit. POCUS was performed within 12 hours of the CXR. The clinical team performing the bedside POCUS were aware of the clinical indication for the CXR but were blinded to the CXR images and radiology report (if available). POCUS images were obtained using a Butterfly IQ+[17] portable ultrasound probe with recorded anonymised images.

POCUS images were obtained using the BLUE protocol[18] and clinical interpretation collected for study purposes only and not reported to the treating clinical team or used to influence patient care.

Data analysis

The recorded POCUS images were analysed by an experienced FUSIC/CACTUS practitioner using only the clinical details provided on the CXR request. This practitioner had not been involved in obtaining any of the POCUS images. Scans were categorised into 'normal' (defined as the presence of a normal pleura with normal pleural sliding in all chest areas, normal distribution of A-lines, presence of <3 B-lines per image window, no evidence of consolidation, effusion or pneumothorax) or 'abnormal', with any significant clinical findings documented. This analysis was then compared with the formal consultant paediatric radiologist report of the CXR for consistency of the findings. When reviewing the formal CXR report, only findings which would have an impact on patient treatment decisions were recorded as 'abnormal' during classification.

The study design was also interested in the role of POCUS in daily patient management decisions where timely reporting of traditional image modalities would be performed by non-radiologists. In most acute clinical situations in a paediatric setting, this would be done by a ward-based paediatric registrar or consultant. To explore this concept, CXRs were also reported independently by two senior paediatric registrars (one from a paediatric intensive care training background and one from a general paediatric training background) and the CXR classified into 'normal' or 'abnormal' with the same criteria.

Sensitivity and specificity of POCUS and CXR reporting were analysed using MedCalc online statistical software (V.20.305[19]).

RESULTS

Participants

102 patients were recruited for the study over the 8-month period, with 2 patients excluded due to incomplete images being available for analysis (figure 1). Demographic data of study participants can be seen in table 1. Participants had an average weight of 23.8 kg (range 2.28–72.4 kg). A summary of the clinical indications for patients requiring CXR and therefore entering the study can be found in figure 2, with the majority being related to respiratory symptoms or as part of an infection screen. When considering the patient cohort included in the study, 35% were previously healthy patients with no significant medical history and 65% had a clinically relevant comorbidities, including prematurity-related chronic lung disease, congenital cardiac disease, diaphragmatic hernia, scoliosis, tracheo-oesophageal fistula and tracheostomies.

Findings

30% (30) of POCUS scans were classified as normal with no clinically significant findings. 97% (29) of these patients also had normal CXR reports. One patient was identified as having an abnormal CXR due to a small pleural effusion which was not noted on POCUS. Further review of these POCUS images identified that while the normal protocol for image collection was performed, the pleural effusion was missed due to a technical error in the recording of one of the images. In this case, the pleural effusion did not require further intervention and was not significant impact in deciding a treatment pathway.

70% (70) of POCUS performed were classified as having abnormal findings when reviewed by the FUSIC/CACTUS practitioner, with 90% of these (63) having consistent findings on the radiologist report. In 4% (3) of cases, conclusions in the CXR and POCUS reports were consistent in the context of the overall diagnosis, but the details of the report commented on a variety of pathological findings, which varied between modalities. This was felt to represent natural subjective interpretation of radiological reporting.

6% (4) POCUS reports identified abnormal findings which were not reported on CXR. This is consistent with other studies which have shown that POCUS can identify pathology earlier in a clinical course than comparable CXR.[20] In all four cases, POCUS identified findings consistent with atelectasis in one or both lower lobes which was not reported on the equivalent CXR. As POCUS interpretations in this study were not being used to guide clinical care, these findings did not alter treatment decisions. Retrospective review determined that these findings were not significant enough to have changed the management of the patients had POCUS been used in clinical decision-making, however these findings support the existing evidence that POCUS may provide earlier visualisation of changes in the lung which can reflect developing or resolving pathology.

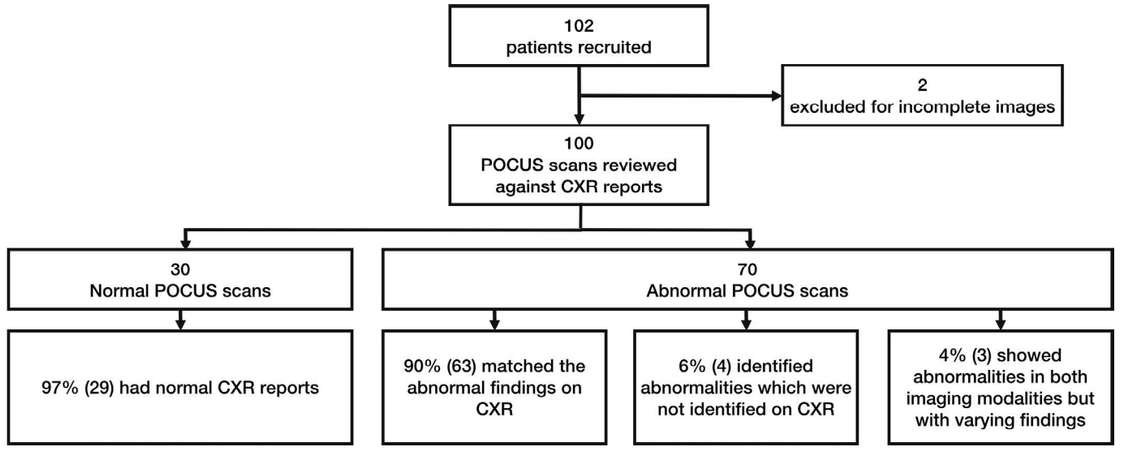

Figure 1 Patient flow diagram. CXR, chest X-ray; POCUS, point-of-care ultrasound.

Statistical analysis shows that POCUS has a sensitivity of 98.51% (95% CI 91.96% to 99.96%) and a specificity of 87.9% (95% CI 71.8% to 96.6%) with diagnostic accuracy of 95% (positive predictive value (PPV) 94.3%, negative predictive value (NPV) 96.7%) when comparing the identification of normal and abnormal findings on CXR.

Lung ultrasound versus paediatric registrar CXR report

When comparing ward-based clinician reporting of CXR with formal radiologist reports, sensitivity of the ward-based clinician was lower at 88.46% (95% CI 79.22% to 94.59%) with specificity of 86.96% (95% CI 66.41% to 97.22%). This was felt to be related to cautious over-reporting by ward-based clinicians with 73% of CXR reported to have abnormal findings compared with 67% of radiologist reports. Diagnostic accuracy was 88.12% (PPV 95.83%, NPV 68.97%).

Quality of POCUS image collection

We had to exclude two patients scans, due to incomplete image recording, which did not allow for assessment of all lung fields. No POCUS studies were excluded due to image quality, although 1% (one study) did miss a small pleural effusion due to an image collection error.

Study limitations

While this study is one of the largest to highlight that normal lung POCUS has high sensitivity and specificity comparable to a normal CXR, it does have some limitations. Due to a small number of POCUS trained personnel and the recognition that the study team were collecting data concurrently with their normal clinical daily work, we could not include every eligible child during the study period. This study was conducted in a large teaching hospital where approximately 350 inpatient CXR are performed monthly. Our study sample reflects approximately 3.7% of these cases but includes a representative spread of patient demographics and clinical conditions.

During data collection, we aimed to collect POCUS images within a 12-hour window of the CXR being performed. Ideally POCUS would have been performed at the same time as the CXR to ensure that image findings were most closely correlated. However, this highlights a real-life issue of access to POCUS trained staff in a general paediatric workplace which will only improve with further adoption of this modality in routine care. Additionally, as a pragmatic study, the protocol also did not set any stipulations for CXR to be performed and decisions were made at the discretion of the clinical team. This may limit the external validity of the findings.

Table 1 Demographic data

Age	Number of patients
>12 years	31
5–11 years	10
1–4 years	27
4–12 months	22
0–3 months	10

DISCUSSION

This study provides several important factors which identify the beneficial use of POCUS in a general paediatric population of patients. The most relevant outcome when considering the adoption of POCUS is the correlation of a normal POCUS study with a normal CXR. Our data demonstrated a 97% correlation of normal POCUS to CXR with 98.5% sensitivity. This indicates that using POCUS as a rapid, ward-based assessment by appropriately trained practitioners can viably reduce the number of CXR performed in paediatric patients of all ages. Movement of paediatric patients between hospital departments is both distressing to the patient and their family[21] and can be logistically challenging when additional medical devices are considered.[12] Reduction in the number of ionising procedures is also essential for young children or those with chronic illness who may be exposed to multiple investigative procedures throughout their life.[22]

This study has also demonstrated a high sensitivity for POCUS (98.5%) in identifying both normal and abnormal lungs when compared with CXR. Our data indicated that POCUS could identify abnormal lungs in 100% of cases when reviewed by an experienced practitioner. Abnormal findings on POCUS correlate with those reported on formal CXR reports and in some cases can identify earlier pathological changes which were not seen on CXR. This aligns with other previous studies.[20]

Our comparison of POCUS with non-radiologist reporting of CXR suggests that POCUS is more sensitive by 10% in identifying normal or abnormal lungs. When considering that most clinical decisions based on traditional imaging techniques are made without formal radiologist reports in the acute setting, our data would indicate POCUS provides a more sensitive assessment in the hands of an experienced practitioner.

We acknowledge that POCUS is still a young imaging modality among general paediatricians. Use of POCUS as a diagnostic tool relies on practitioners developing an experience base to be able to use it confidently for decision making in treatment pathways. Our study has demonstrated that with appropriate training, POCUS can be reliably used to identify the absence of lung pathology and therefore reduce the need for ionising radiology investigations in all children. Developing this in clinical practice has the potential to reduce the need to move children to facilitate investigations and would enable a faster and more efficient diagnostic pathway for respiratory pathology. As paediatric practice in hospitals continues to encourage the role of advanced nurse practitioners to practice alongside the paediatric medical teams, our study has

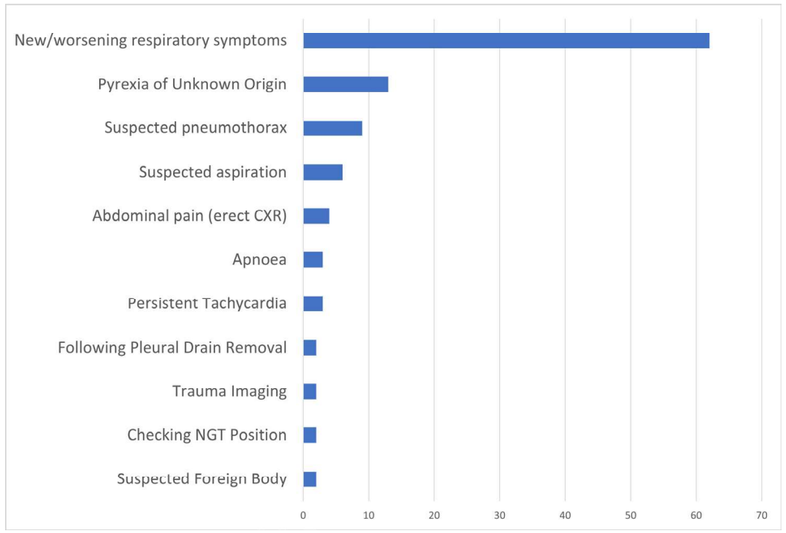

Figure 2 Clinical indications for chest X-ray (CXR) being performed.

also demonstrated the importance of expanding this modality to all practitioners who are involved in the acute assessment of paediatric patients.

In intensive care settings, POCUS is often considered as an extension of the clinical examination rather than a focused radiological diagnostic investigation. Further study would be warranted to compare the findings of clinical examination with POCUS in routine clinical assessment of patients in a ward-based setting. We also acknowledge that many CXRs are performed on children for reasons which are not related to respiratory illness, such as nasogastric tube placement, concerns about free air in the abdomen or for assessment of mediastinal or cardiac structures. POCUS has the potential to provide vital information which may also correlate with CXR in these circumstances and further research should focus on the potential of POCUS in other clinical situations.

CONCLUSIONS

POCUS can be safely, accurately and easily performed by trained members of the paediatric MDT in the ward environment. POCUS is highly sensitive and specific when compared with CXR, with strong PPV and NPV for normal and abnormal CXRs. POCUS can play an important role in reducing CXR use and speeding up identification of respiratory pathology in children.

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Ethics approval This study was registered with the paediatric clinical governance group and was assessed to not require further ethics approval as point-of-care ultrasound images were obtained for analysis purposes only and did not influence clinical management in any cases. Chest X-ray was performed based on clinical need only (decided by the attending clinicians). All patients and/or guardians provided written consent to take part in the study.
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ARTIGO ORIGINAL

Valor preditivo das medidas de função pulmonar para risco cardiovascular: um grande estudo de coorte prospetivo

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RESUMO

Introdução Embora as medidas de função pulmonar estejam associadas a doenças cardiovasculares (DCV), os valores preditivos adicionais destas medidas permanecem pouco claros.
Métodos A partir do UK Biobank, foram incluídos 308 415 participantes sem DCV com parâmetros espirométricos. Os resultados de DCV incluídos foram definidos pelos modelos de previsão QRISK3 da American College of Cardiology/ American Heart Association (ACC/AHA) e da European Systematic Coronary Risk Evaluation (SCORE), respetivamente. Foram utilizados modelos de riscos proporcionais de Cox para estimar as associações entre medidas de função pulmonar e resultados de DCV. A capacidade preditiva foi determinada pelas análises da curva de decisão.
Resultados Durante um seguimento médio de 12,5 anos, foram registados 21 885 eventos QRISK3, 12 843 eventos ACC/AHA e 2987 eventos SCORE. As associações dos parâmetros espirométricos com os resultados de DCV apresentaram-se em forma de L. As insuficiências restritivas e obstrutivas foram associadas a HR ajustados de 1,84 (IC 95%: 1,65 a 2,06) e 1,72 (IC 95%: 1,55 a 1,90) para a DCV SCORE, respetivamente, em comparação com a espirometria normal. Foram observadas associações similares para a DCV QRISK3 (restritiva vs. normal, HR ajustado: 1,30, IC 95%: 1,25 a 1,36; obstrutiva vs. normal, HR ajustado: 1,20, IC 95%: 1,15 a 1,25) e DCV ACC/AHA (restritiva vs. normal, HR ajustado: 1,39, IC 95%: 1,31 a 1,47; obstrutiva vs. normal, HR ajustado: 1,26, IC 95%: 1,19 a 1,33). A utilização de modelos que integram o volume expiratório forçado não linear em 1 segundo conduziu a benefícios líquidos adicionais a 10 anos por cada 100 000 pessoas de 25, 43 e 5 para a DCV QRISK3 no limiar de 10%, DCV ACC/AHA a 7,5% e DCV SCORE a 5,0%, respetivamente.
Conclusão Os médicos podem ter em consideração os indicadores espirométricos na avaliação do risco de DCV. São necessários estudos de custo-eficácia e ensaios clínicos para pôr em prática a nova avaliação de risco de DCV.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Lung function impairments, respiratory diseases and spirometry parameters are associated with a higher risk of cardiovascular diseases (CVDs). However, whether these lung function measures provide additional prediction values for CVD risk prediction remains unclear.

WHAT THIS STUDY ADDS

► The addition of lung function indicators in non-fatal and fatal CVD risk prediction models, especially forced expiratory volume in 1 s and forced vital capacity, offered a slight improvement for 10-year CVD risk prediction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study indicates that clinicians could consider lung function measures in CVD risk assessment and consider improving lung function as a target for CVD prevention. However, further evidence is needed using cost-effectiveness analysis or clinical trial design to determine the performance of new CVD risk models that integrate spirometry measures in clinical practice.

INTRODUCTION

Observational studies show that impaired lung function and subclinical impairments are associated with a higher risk of cardiovascular disease (CVD).[1–5] Furthermore, Mendelian randomisation studies suggest that reduced forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) are independently and causally associated with coronary artery disease and reverse causations are not found.[6 7] Preventing lung function impairment and reducing exacerbation of chronic obstructive pulmonary disease (COPD) may contribute to CVD prevention.[8] Therefore, lung function parameters could be used as potential predictors and prevention targets for CVD. Spirometry tests are recommended for confirmation of COPD screening among symptomatic and/or at-risk individuals in primary care.[9] This further provides the possibility to add spirometry measures for CVD risk evaluation. On the other hand, the benefit of CVD prevention may increase the cost-effectiveness of spirometry tests. Considering the sequelae in respiratory and cardiovascular systems following COVID-19, accurate CVD risk prediction integrated with lung function surveillance is more practical and is essential to avoid excess future CVD events.[10 11] However, whether lung function impairment screening by spirometry contributes to CVD risk assessment in the general population remains uncertain.

Currently, several fatal and non-fatal CVD prediction models that integrated with conventional CVD risk factors are used for primary prevention and health promotion, including the QRISK3 risk score,[12] the American College of Cardiology/ American Heart Association (ACC/AHA) CVD risk score[13] and the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score.[14] However, lung function measures do not feature in the aforementioned CVD risk prediction models. The lack of data from a single large cohort with consistent phenotyping of multiple exposures and events

limits research on this topic. This issue requires better evidence to inform clinical care.

In this study, by investigating the UK Biobank, we aimed to (1) detect the changes in predictive discrimination of CVD risk prediction models with lung function measures and impairment patterns compared with the original CVD risk prediction models; (2) compare the predicted value of lung function parameters to determine the most suitable measures in CVD risk evaluation.

METHODS

Population

Data of this study were from the UK Biobank, one of the largest open cohorts, with half a million participants aged 37–73 years recruited from 22 assessment centres across England, Wales and Scotland from 2006 to 2010. Details of this cohort were described elsewhere.[15] Briefly, the sociodemographic characteristics, lifestyle factors, family histories and medical histories were collected via a touchscreen questionnaire or a verbal interview at the assessment centre from 2006 to 2010. Physical measures and biological sampling, including spirometry tests, were also conducted at recruitment. The medical histories of participants were derived from the first occurrence dates of diseases before the recruitment. The first occurrences of diseases were generated from hospital admission records, death register records and self-report questionnaires.[16] The UK Biobank received ethics approval from the North West Multicenter Research Ethics Committee (reference number 11/NW/03820). People were followed to get their health outcomes with their consent. In this study, we excluded participants who withdrew consent (n=141), those diagnosed with CVDs at baseline (n=18 989), those without valid spirometry data (n=1 22 619), those with missing values in variables for the calculation of lung function parameters using the Global Lung Function Initiative (GLI) 2012 equations (n=1847) and those who had missing values in conventional CVD risk factors (n=50 496). After exclusions, a total of 308 415 participants were included (online supplemental figure S1). Baseline characteristics and CVD factors among participants with and without spirometry data are listed in online supplemental table S1. The inclusion criteria for the current analyses were similar to those used in the development of the original CVD prediction models.

Lung function and chronic respiratory disease status

Breath spirometry was tested using the Vitalograph Pneumotrac 6800 spirometer by trained healthcare technicians and nurses in UK Biobank assessment centres following the UK Biobank procedure manual.[17] Participants were asked to record two blows (lasting for at least 6 s) within about 6 min. The third blow was required if the results of the first two blows were unacceptable (defined as a ≥5% difference). A blow was deemed valid if: (1) the extrapolated volume at the start of the test is excessive, (2) the time to peak flow is excessive, (3) an adequate plateau at the end of the test does not exist, (4) cough was detected during the manoeuvre, (5) the test is less than 6 s, (6) the test was explicitly not accepted by the investigator or (7) the test was explicitly rejected by the investigator. The highest values for spirometry parameters from acceptable and valid blows were used in analyses.[18]

The lung function parameters evaluated in this study include FEV_1, FVC, peak expiratory flow (PEF) and FEV_1/FVC ratio. Further, absolute spirometry measurements (FEV_1, FVC) were converted to % predicted values based on demographic data (age, height, gender and ethnicity) using the GLI-2012 equation.[19] Lung function impairment patterns were classified into clinically meaningful groups: normal spirometry (both the FEV_1/FVC ratio and FVC at or above the lower limits of normal (LLN)), obstructive impairment (FEV_1/FVC<LLN) and restrictive impairment (FEV_1/FVC≥LLN and FVC<LLN).[20] LLNs for spirometry parameters were calculated using the GLI-2012 equations. The GLI R-macro was used for the GLI-2012 equation calculations.[21]

In addition, chronic respiratory disease status at baseline was included as a new predictor. Chronic respiratory disease was defined as having COPD (International Classification of Diseases ICD-10 code: J41–J44) or asthma (ICD-10 code: J45–J46) at baseline determined by self-report, hospital inpatient data and death data.

Outcomes defined

Data on health outcomes were from the linkage to hospital admission records and death registry records. There were three main outcomes considered in this study according to current CVD prediction models. (1) Composite QRISK3 CVD events used as outcomes in the QRISK3 prediction model, including fatal or non-fatal coronary heart disease, ischaemic stroke or transient ischaemic attack (ICD-10 code: G45, I20–24 and I63–64)[12]; (2) composite ACC/AHA CVD events, a composite of fatal and non-fatal CVD that reflects the ACC/AHA guideline prediction score including death from CVD (ICD-10 code: I20–25 and I60–64) or hospitalisation for CVD (ICD-10 code: I21, I22 and I60–64)[13] and (3) fatal SCORE CVD events, fatal CVD as defined by primary cause of death from events included in the SCORE clinical guidelines (ICD-10 code: I10–15, I44–51, I20–25 and I61–73).[14]

Covariates

The conventional risk factors at recruitment included in each risk prediction model were used to calculate individual CVD risk scores in this study. In the QRISK3 prediction model, risk factors include age, sex, systolic blood pressure (SBP), smoking (current, previous or never), ethnicity (white, black, south Asian or mixed/others), Townsend Deprivation Index (TDI) (index of deprivation based on postcode), total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio, body mass index (BMI), family history of CVD, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3–5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medication use and cholesterol-lowering medication use. In ACC/AHA or SCORE risk models, risk factors include age, sex, ethnicity (white, black, South Asian or mixed/other), smoking (current, previous or never), total cholesterol, HDL-C, SBP, diastolic blood pressure, antihypertensive medication use and cholesterol-lowering medication use.

Statistical analysis

Descriptive characteristics of all participants according to lung function impairment patterns were presented as means with SDs or medians with IQRs for continuous variables and frequencies with percentages for categorical variables.

The follow-up duration started at the date of the spirometry assessment and ended with the first date of hospitalisation for non-fatal CVD, the date of death, the date lost to follow-up or the end of follow-up (30 September 2021 for England, 19 September 2021 for Scotland and 31 May 2016 for Wales), whichever came first. The crude event incidence rates and 95% CIs according to lung function impairment patterns were calculated using Poisson regression models. Cox proportional hazard models were used to estimate HRs and 95% CIs for CVD outcomes adjusted for 10-year individual CVD risk scores calculated from three aforementioned prediction models. Restricted cubic spline (RCS) models with four knots at the 5th, 35th, 65th and 95th percentiles were used to evaluate the non-linear relationships between spirometry parameters and CVD outcomes adjusted for individual risk scores.[22] A non-linearity test used the likelihood ratio to compare the model that comprised the linear term with the model that comprised both the linear and the cubic spline terms. The reference points in the RCS models were the medians for FEV_1 (2.76 L), FVC (3.64 L) and PEF (400.00 L/min) and clinically relevant reference points for FEV_1/FVC (0.70), FEV_1 % predicted (80%) and FVC % predicted (100%).[23] For sensitivity analyses of non-linear relationships, generalised additive models (GAM) were used. The generalised cross-validation criterion was used to solve the optimal effective degree of freedom used in each model. The change in Harrell's concordance statistic (C-statistic) was used to estimate the added discriminative ability of non-linear spirometry indicators and lung function impairment category to the original prediction models.[24 25] In addition to the changes in C-statistic, the decision curve analysis (DCA) was used to assess the clinical utility.[26 27] The DCA was used to evaluate and compare the net benefits of models with and without lung function measures for 10-year CVD risk prediction from a clinical utility perspective.[28 29] The net benefits of the 10-year CVD risk prediction models with and without lung function measures were calculated at the thresholds of 10.0%, 7.5% and 5.0% for QRISK3, ACC/AHA and SCORE models, respectively.[12–14] Locally weighted scatterplot smoothing (LOESS) was used to derive the smooth decision curves. For internal validation, the changes in the C- statistics and net benefits were recalculated in two randomly assigned subdatasets with 70% and 30% of the total participants.

For sensitivity analysis, we imputed the variates for the GLI-2012 equations with the means for continuous variables (height) and indicators for missing category variables (ethnicity). Multiple imputations with five replications were used to impute other predictors with missing values based on a chained equation method. The missing cases and proportions of covariates are listed in online supplemental table S2. In subgroup analysis, we investigated the magnitudes of the association between lung function impairment patterns with CVD outcomes and the model performances among participants in different age groups (<60 and ≥60 years) and sexes (females and males).

Statistical analyses were conducted using Stata (V.15, StataCorp) and R (V.4.2.0). All tests were two-sided with a significance level of 0.05.

Table 1 Baseline characteristics of participants according to lung function impairment patterns (N=3 08 415)

Characteristics	All participants (N=3 08 415)	Normal spirometry (n=2 58 408)	Restrictive impairment (n=21 999)	Obstructive impairment (n=28 008)
Age, years, mean (SD)	56.15 (8.05)	56.22 (8.01)	55.21 (8.14)	56.29 (8.23)
Male, no (%)	142 304 (46.1)	117 294 (45.4)	10 960 (49.8)	14 050 (50.2)
White, no (%)	293 928 (95.3)	248 474 (96.2)	19 113 (86.9)	26 341 (94.0)
Townsend Deprivation Index at recruitment, median (IQR)	−2.24 (−3.70, 0.30)	−2.33 (−3.74, 0.10)	−1.64 (−3.39, 1.38)	−1.67 (−3.43, 1.34)
Smoking status, no (%)				
Never	168 660 (54.7)	144 628 (56.0)	12 238 (55.6)	11 794 (42.1)
Previous	108 050 (35.0)	91 188 (35.3)	7043 (32.0)	9819 (35.1)
Current	31 705 (10.3)	22 592 (8.7)	2718 (12.4)	6395 (22.8)
Body mass index, kg/m^2, mean (SD))	27.33 (4.65)	27.24 (4.50)	29.54 (5.68)	26.48 (4.57)
Systolic blood pressure, mmHg, mean (SD)	137.82 (18.44)	137.71 (18.38)	139.40 (18.71)	137.60 (18.66)
Diastolic blood pressure, mmHg, mean (SD)	82.42 (10.03)	82.36 (9.99)	83.86 (10.26)	81.78 (10.08)
Total cholesterol, mmol/L, mean (SD)	5.75 (1.12)	5.77 (1.11)	5.60 (1.16)	5.67 (1.11)
HDL-C, mmol/L, mean (SD)	1.46 (0.38)	1.47 (0.38)	1.35 (0.36)	1.47 (0.39)
Total cholesterol-to-HDL-C ratio, mean (SD)	4.14 (1.12)	4.13 (1.11)	4.36 (1.18)	4.06 (1.12)
Family history of CVD, no (%)	172 038 (55.8)	145 057 (56.1)	12 103 (55.0)	14 878 (53.1)
Antihypertensive medication use, no (%)	56 381 (18.3)	45 385 (17.6)	5788 (26.3)	5208 (18.6)
Cholesterol-lowering medication, no (%)	44 531 (14.4)	35 943 (13.9)	4553 (20.7)	4035 (14.4)
Chronic respiratory diseases, no (%)	37 403 (12.1)	25 348 (9.8)	3163 (14.4)	8892 (31.7)
Lung function indicators				
FVC, L, mean (SD)	3.76 (1.00)	3.86 (0.95)	2.72 (0.70)	3.66 (1.15)
FEV_1, L, mean (SD)	2.84 (0.79)	2.97 (0.74)	2.10 (0.57)	2.26 (0.79)
PEF, L/min, mean (SD)	414.86 (125.83)	432.58 (120.34)	335.58 (105.90)	313.66 (117.69)
FEV_1/FVC, mean (SD)	0.76 (0.07)	0.77 (0.05)	0.77 (0.05)	0.61 (0.07)
FEV_1 % predicted, mean (SD)	92.68 (16.70)	97.02 (13.08)	67.48 (9.23)	72.38 (18.47)
FVC % predicted, mean (SD)	96.63 (15.49)	99.39 (12.76)	69.10 (8.06)	92.73 (20.22)

CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL-C, high-density lipoprotein cholesterol; PEF, peak expiratory flow.

RESULTS

Of 308 415 people without CVD at baseline and complete data on covariates included in this study, 21 885 developed QRISK3 composite CVD events, 12 843 developed ACC/AHA composite CVD events and 2987 developed SCORE fatal CVD events over a median follow-up of 12.5 (IQR: 11.8–13.2) years. The analysis sample comprised 142 304 (46.1%) males, and the mean age was 56.15 (±8.05) years. The mean values of FVC, FEV_1, PEF and FEV_1/FVC were 3.76±1.00 L, 2.84±0.79 L, 414.86±125.83 L/ min and 0.76±0.07, respectively. Of all participants included, 21 999 (7.1%) were classified as restrictive impairment, and 28 008 (9.1%) were classified as obstructive impairment. The baseline characteristics of participants according to lung function impairment patterns are listed in table 1. Participants with normal spirometry were more likely to be females, whites, non-smokers, have lower TDI (less deprived), higher total cholesterol, higher HDL-C, higher probability of family history of CVD, lower probability of antihypertensive medication use and cholesterol-lowering medication use. The baseline risk characteristics of participants according to the CVD status at the end of follow-up are listed in online supplemental table S3. All spirometry parameters were correlated as shown in online supplemental figure S2. The strongest correlation was detected between FEV_1 and FVC (r=0.95), and the weakest correlation was detected between FEV_1/FVC ratio and FVC (r=0.01). The distributions of spirometry parameters were plotted in online supplemental figure S3.

According to RCS splines (figure 1 and online supplemental figure S4), the associations of spirometry parameters with fatal and non-fatal CVD were reversed L-shape. Lower spirometry measures were associated with higher risks of all CVD outcomes, whereas higher lung function parameters did not show higher protective effects. The magnitudes of effects for fatal SCORE CVD outcome were stronger, followed by composite ACC/AHA CVD and composite QRISK3 CVD. The non-linear splines using GAM showed similar L-shapes (plateaus or decrease of HRs at extreme lower ranges), as well as the RCS splines among 360 758 participants with imputed missing values in covariates (online supplemental figures S5 and S6).

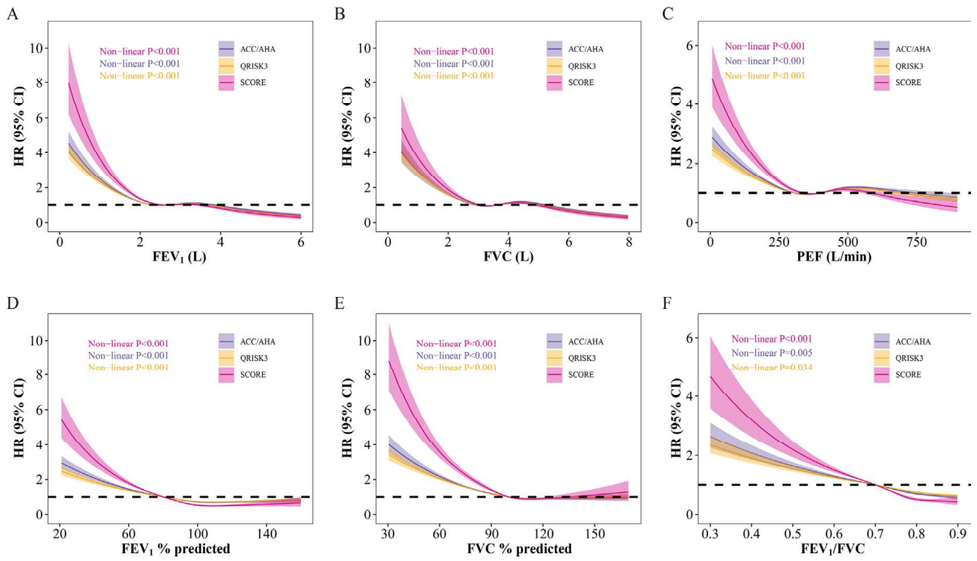

Figure 1 The non-linear associations of spirometry indicators with composite CVD and fatal CVD outcomes according to restrictive cubic splines. Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. The reference points are the medians for FEV_1 (2.76 L), FVC (3.64 L), PEF (400 L/min) and clinically significant reference points for FEV_1/FVC (0.7), FEV1 % predicted (80%) and FVC % predicted (100%). Individual risk scores from three prediction models are adjusted in each model. Risk factors in the QRISK3 model include age, sex, systolic blood pressure, smoking, ethnicity, Townsend Deprivation Index, total cholesterol to high-density lipoprotein cholesterol ratio, body mass index, family history of CVD, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3–5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medications and cholesterol-lowering medication use. In ACC/AHA or SCORE risk models, covariates include age, sex, ethnicity, smoking, total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, antihypertensive medications and cholesterol-lowering medication use. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

Participants with chronic respiratory diseases had 15% (95% CI: 11% to 19%), 15% (95% CI: 9% to 21%) and 28% (95% CI: 16% to 42%) higher risks of composite QRISK3 CVD, composite ACC/AHA CVD and fatal SCORE CVD, respectively, after adjusting for predicted individual risks calculated from the original prediction models (figure 2 and online supplemental table S4). Compared with normal spirometry, restrictive and obstructive impairment were associated with HRs of 2.20 (95% CI: 1.97 to 2.46) and 1.93 (95% CI: 1.74 to 2.13) for fatal SCORE CVD after adjusting for age and sex (figure 2). After adjusting for predicted individual CVD risk calculated using the original SCORE prediction model, the effect sizes were attenuated (adjusted HR: 1.84 (95% CI: 1.65 to 2.06) for restrictive impairment and adjusted HR: 1.72 (95% CI: 1.55 to 1.90) for obstructive impairment). Similar associations were observed for composite ACC/AHA CVD and composite QRISK3 CVD, while the effect sizes were larger for fatal SCORE CVD outcomes. The magnitudes of these associations were slightly increased among the 360 758 participants with imputed missing values in covariates (online supplemental table S5). Significant interactions were identified between chronic respiratory disease status, lung function impairment and sex for composite QRISK3 CVD and composite ACC/AHA CVD (online supplemental table S6). The effect sizes were larger among females. The associations were consistent among participants aged <60 years and those aged ≥60 years, except for prevalent chronic respiratory diseases, which were associated with a higher risk of composite ACC/AHA CVD among participants aged ≥60 years (online supplemental table S7).

Conventional risk factors in the original models yielded a C-statistic of 0.7385 (95% CI: 0.7355 to 0.7416) composite QRISK3 CVD, a C-statistic of 0.7303 (95% CI: 0.7263 to 0.7344) composite ACC/AHA CVD and a C-statistic of 0.7969 (95% CI: 0.7895 to 0.8043) fatal SCORE CVD using data from the UK Biobank (online supplemental table S8). All lung function measures significantly improved the discrimination, with the largest improvement seen with non-linear FEV_1 (C-statistic change: +0.0018 for composite QRISK3 CVD, +0.0033 for composite ACC/AHA CVD) or non-linear FEV_1 % predicted (+0.0065 for fatal SCORE CVD). The changes in the C-statistics were largely consistent with results among 360 758 participants with imputed missing values (online supplemental table S9) and in the two validation datasets (baseline characteristics: online supplemental table S10, results of C-statistics: online supplemental tables S11 and S12) except for the addition of chronic respiratory diseases.

According to the decision curve analysis within 10 years, all models that integrated lung function measures had higher net benefits than the original models (table 2). At the recommended thresholds, using the model that integrated non-linear FEV_1 led to a net increase of 25 more true-positive (TP) composite QRISK3 events, 43 more TP composite ACC/AHA events and 5 more TP fatal SCORE events per 100 000 participants without an increase in the number of false-positive cases compared with the original models. From the false-positive reduction perspective, using the new models that integrate non-linear FEV_1 would lead to the equivalent of 224, 391 and 48 fewer redundant interventions per 1 00 000 patients, respectively, in participants who would not develop CVD within 10 years. In addition, this would lead to no increase in the number of untreated future CVD cases. The largest advantage of net benefit was observed with the model that integrated with non-linear FEV_1 and non-linear FVC. The results were consistent in sensitivity analysis among 360 758 participants with imputed missing values and two internal validation subsets (online supplemental tables S13–S15). The advantage of net benefit of SCORE model was not shown among females (online supplemental tables S16 and S17). The advantages of net benefits of models that integrated with lung measures were much higher among participants aged 60 and older (online supplemental tables S18 and S19).

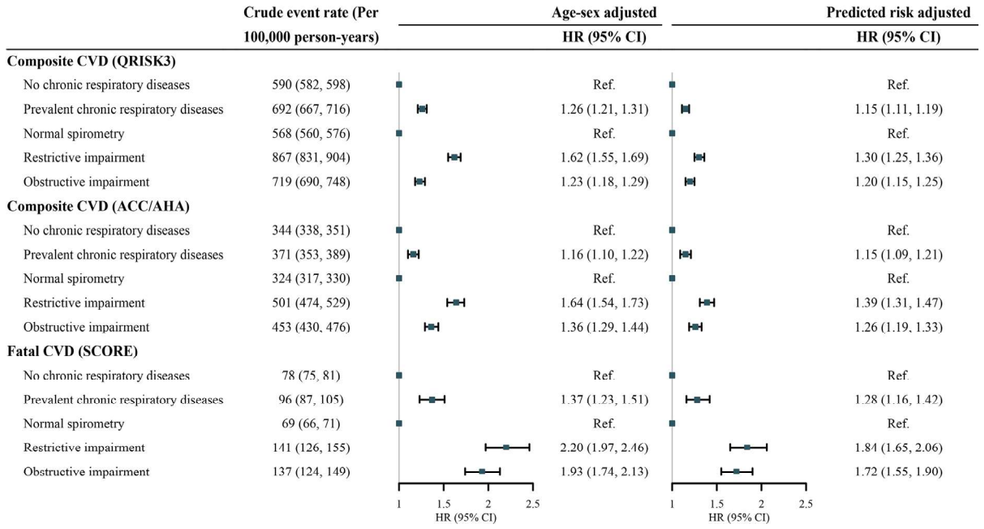

Figure 2 The association of lung function impairment with composite CVD and fatal CVD outcomes. Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. Individual CVD risk scores were calculated from three prediction models. Risk factors in the QRISK3 model include age, sex, systolic blood pressure, smoking, ethnicity, Townsend Deprivation Index, total cholesterol to high-density lipoprotein cholesterol ratio, body mass index, family history of CVD, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3–5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medications and cholesterol-lowering medication use. In ACC/AHA or SCORE risk models, covariates include age, sex, ethnicity, smoking, total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, antihypertensive medications and cholesterol-lowering medication use. CVD, cardiovascular disease.

Figure 3 shows the decision curves for CVD prediction models that integrated non-linear FEV_1 or non-linear FVC. Across the likely threshold probability (1–15% for QRISK3, 1–10% for ACC/AHA and 1–8% for SCORE), CVD prediction models with non-linear FEV_1 and non-linear FVC showed slightly higher net benefits than the original models. The figure of unsmoothed, original DCA curves is listed in online supplemental figure S7). The nomograms of three CVD prediction models that integrated with non-linear FEV_1 or non-linear FVC are listed in online supplemental figures S8–S13).

DISCUSSION

With this large and comprehensive UK Biobank cohort, our study evaluated the additional prediction values of spirometry parameters for CVD risk prediction. Over a median of 12.5 years of follow-up, lung function impairments and lower spirometry parameters were associated with higher risks of non-fatal and fatal CVD outcomes after adjusting for the predicted 10-year CVD risk score. The associations of spirometry parameters with CVD outcomes tended to be L-shaped. The addition of some spirometry parameters could improve the discrimination of the original prediction models, with the largest improvement seen with FEV_1. From a clinical utility perspective, the addition of FEV_1 and FVC could lead to higher net benefits. Our study suggests that spirometry parameters, especially FEV_1 and EVC, could serve as risk factors for the identification of high-risk individuals of composite and fatal CVD events for primary prevention.

Consistent with previous studies, our study supports the association of lung function with fatal and non-fatal CVD. According to the Coronary Artery Risk Development in Young Adults study, per 10-unit decrement in FEV_1 % predicted and per 10-unit decrement FVC % predicted were associated with an 18% and a 19% higher risk of future cardiovascular events, respectively, independent of classic cardiovascular risk factors.[30] Restricted spirometry was associated with a 54% higher risk of CVD after adjusting for cardiometabolic risk factors.[3] Subclinical reductions in FEV_1/FVC and FVC % predicted differentially associated with cardiac function and heart failure risk in late life.[31] A previous study showed that the highest quintile of FEV_1 and FVC were related to a 30% and 21% risk reduction, respectively, of cardiovascular risk among patients with COPD.[32] Moreover, our results also show that the association of lung function impairment with fatal CVD is stronger than composite CVD outcomes. This suggests that lung function indicators are more sensitive to fatal CVD risk prediction than non-fatal CVD.

According to the L-shaped associations of spirometry indicators with CVD risk, we found that impaired lung function was associated with higher risks of fatal and non-fatal CVD, but better lung function was not related to lower CVD risks. This evidence supports the high-risk/symptomatic screening strategy of COPD case-finding.[8] COPD screening might provide the foundation and data resources for spirometry tests, which might also benefit CVD risk assessment. Lambe et al[9] suggested that regular systematic case-finding for COPD is likely to be cost-effective in the long term. However, the aforementioned study did not take into account the reduction of comorbidities, such as CVD, as a potential benefit, which might underestimate the cost-effectiveness of screening. What's more, a study suggested that the greater effectiveness of spirometry screening exists in identifying and targeting people who had undiagnosed COPD or subclinical lung function impairments and early prevention and detection of signs of lung damage were needed.[33] Thus, lung function measures could be taken into consideration when assessing CVD risk and considered as potential targets for reducing CVD burden. However, further studies are needed to confirm the specific high-risk populations for lung function tests.

Accurate prediction of CVD risk is essential in clinical practice to target high-risk populations for healthy lifestyle promotion and cholesterol-lowering or blood pressure-lowering treatment. According to our results, by adding non-linear FEV_1 into the 10-year CVD risk prediction models, 25, 43 and 5 more TP CVD events per 100 000 participants would be identified without increases in the number of false-positive cases compared with the original prediction models. From the false-positive reduction perspective,

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Table 2 Net benefits of models for composite CVD and fatal CVD 10-year risk prediction

Model	Net benefit*	Advantage of model	
		Advantage of net benefit per 100 000 participants	Reduction in avoidable false positive cases per 100 000 participants
Composite CVD (QRISK3)			
Original model	0.00850		
+ FEV_1	0.00875	25	224
+ FVC	0.00874	24	212
+ FEV_1 % predicted	0.00872	21	192
+ FVC % predicted	0.00872	22	196
+ Lung function category	0.00864	14	127
+ PEF	0.00859	9	80
+ Chronic respiratory diseases	0.00854	3	31
+ FEV_1/FVC	0.00856	6	55
Composite CVD (ACC/AHA)			
Original model	0.00168		
+ FEV_1	0.00212	43	391
+ FVC	0.00205	36	327
+ FEV_1 % predicted	0.00194	26	234
+ FVC % predicted	0.00200	31	282
+ Lung function category	0.00181	12	110
+ PEF	0.00189	20	184
+ Chronic respiratory diseases	0.00173	5	46
+ FEV_1/FVC	0.00175	7	63
Fatal CVD (SCORE)			
Original model	0.00005		
+ FEV_1	0.00011	5	48
+ FVC	0.00012	7	63
+ FEV_1 % predicted	0.00011	5	47
+ FVC % predicted	0.00011	6	51
+ Lung function category	0.00007	1	12
+ PEF	0.00008	2	20
+ Chronic respiratory diseases	0.00006	0	3
+ FEV_1/FVC	0.00007	1	12

The threshold of 'high' and 'low' classification for the three prediction models are 10.0% (QRISK3), 7.50% (ACC/AHA) and 5.0% (SCORE). Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. The lung function category includes normal spirometry (reference), restrictive impairment and obstructive impairment. Other spirometry indicators are added to the prediction models as non-linear parameters.

*Net benefit for 10-year CVD risk is calculated as (TP−wFP)/N, where TP is true-positive count, FP is false-positive count, N is the total count of participants, w is the weight of the relative harm of a false-positive and a false-negative result, which is calculated as (1−p)/p, where p is the threshold probability mentioned above (10.0% for QRISK3, 7.50% for ACC/AHA and 5.0% for SCORE). The net benefits under treat all strategy are −0.04949 for composite QRISK3 CVD, −0.04254 for composite ACC/AHA CVD and −0.04611 for fatal SCORE CVD at these thresholds.

CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

redundant interventions in participants who have no CVD risk within 10 years could be avoided. Although these improvements seem modest, a large number of high-risk people would be identified accurately, leading to intervention to prevent or delay CVD events, when multiplying these values by the huge population receiving CVD risk assessment. Moreover, avoidable interventions for non-CVD cases would be reduced to save healthcare budgets. To date, over 758 million people worldwide have had COVID-19,[34] and long-term respiratory complications might follow and require persistent respiratory follow-up.[10]

Thus, it is of great importance to consider adding lung function measures into CVD risk scores to prevent an excess future CVD burden.[11] However, according to the DCA curves, the net benefits of new prediction models that integrated with lung function measures might be modest and might not offset the cost of staff and devices. Thus, cost-effectiveness studies and clinical trials are still needed for confirmation of the performance of CVD risk assessments based on these models in clinical practice.

There are several potential mechanisms underlying these associations. Lung function impairment would increase levels of oxidative stress and systemic inflammation,[35 36] which would affect the vascular endothelium function and cause structural changes in the endothelium contributing to the formation and complication of atherosclerotic lesions.[37] Moreover, impaired lung function might indicate undiagnosed or preclinical COPD, which could induce higher levels of haematocrit and haemoglobin, and could predispose to CVD by elevation in the plasma viscosity.[38 39] According to a two-sample bidirectional Mendelian randomisation study, FEV_1 and FVC tend to be causal risk factors for CVD, and no strong evidence for reverse causation was discovered.[7] More mechanisms

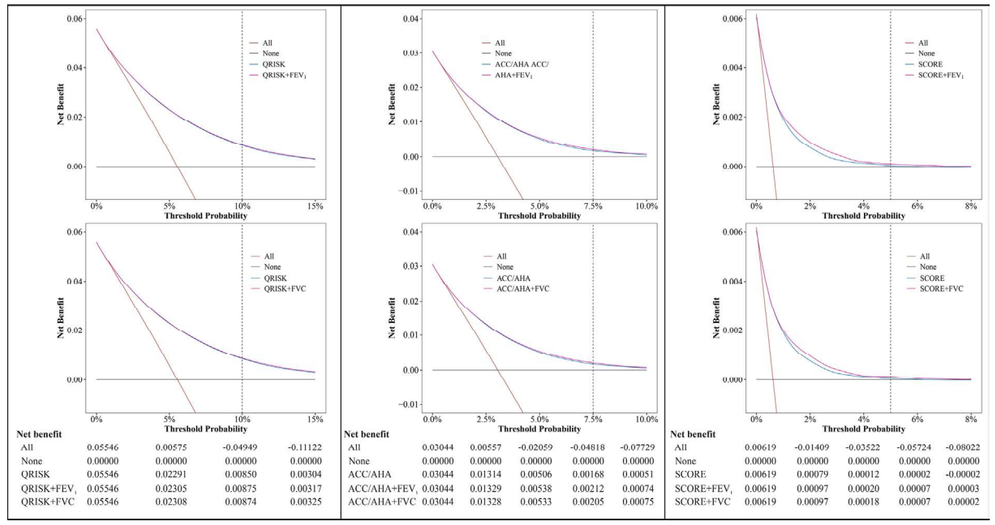

Figure 3 Decision curve analysis of three prediction models that integrated with lung function impairment or parameters for 10-year composite CVD and fatal CVD risks. Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. FEV_1 and FVC are added to the prediction models as non-linear parameters. The tables of net benefits listed under the figures are derived from decision curve analyses. The decision curves were smoothed using the locally weighted scatterplot smoothing (LOESS) method. The y-axis shows the net benefit for 10-year CVD risk prediction. The net benefit is calculated as (TP−wFP)/N, where TP is true-positive count, FP is false-positive count, N is the total count of participants, w is the weight of the relative harm of a false-positive and a false-negative result, which is calculated as (1−p)/p, where p is the x-axis. The dashed vertical lines are the threshold of 'high' and 'low' classification for the three original prediction models (10.0% for QRISK3, 7.50% for ACC/AHA and 5.0% for SCORE). CVD, cardiovascular disease; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.

underlying the associations of spirometry parameters with CVD need to be studied.

Our study contributes to improving the discriminations of current CVD risk prediction models by adding lung function indicators and suggesting FEV_1 and FVC as better risk factors among all spirometry parameters. Several studies have discussed the improvement of current CVD risk prediction models. Welsh et al[40] suggested that although people with diagnosed or undiagnosed baseline diabetes had higher risks of CVD, the addition of circulating hemoglobin A1c in prediction models did not increase reclassification. Previous studies indicated that lipoprotein (a), grip strength, usual walking pace, and grip strength and walking pace combined could improve the identification of high-risk individuals of CVD.[41 42] Lung function measures could result in similar and even better discriminations for CVD risk prediction. Moreover, spirometry is a reproducible and objective measurement of lung function. The conduction of spirometry is non-invasive, readily available and easily performed in any healthcare setting, which could be an advantage for accurate CVD risk prediction.[43]

Strength and limitations

To the best of our knowledge, the present study is the largest study to assess the prediction value of lung function parameters on CVD outcomes adjusted for all conventional risk factors. This study used comprehensive and standard cohort data from the UK Biobank. The C-statistics of CVD risk models and the baseline characteristics of participants in our study were comparable with those in the original prediction models. Thus, our results were reliable. However, there are several limitations in the present study. Participants in the UK Biobank were healthier than the general population, which might cause healthy volunteer bias. Due to the L-shaped non-linear associations between spirometry parameters and CVD risk, better performance of additional prediction value is likely in the general population. Secular trends in lung function might be a more valuable indicator for CVD prediction,[44] but these data were not accessible in the UK Biobank. Our results should be generalised with caution since no external validation was performed. Further studies using other cohorts and other designs are needed.

CONCLUSION

This study suggests that lung function impairments (restrictive and obstructive) and lower spirometry parameters are associated with composite and fatal CVD outcomes after adjusting for all conventional risk factors. The associations of spirometry parameters with CVD outcomes (composite QRISK3 CVD, composite ACC/AHA CVD and fatal SCORE CVD) tended to be L-shaped. The association was strongest for fatal SCORE CVD. All spirometry parameters could improve discrimination of the prediction models, with the largest improvement seen with FEV_1. Models that integrate FEV_1 and FVC offered additional net benefits compared with the original models. Therefore, FEV_1 and FVC could serve as risk factors in the identification of high-risk individuals with composite and fatal CVD events and be a target for primary prevention and treatment.

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Contributors YaW conceived and designed the study. LHZ conducted the data analysis and interpreted the results assisted and supervised by HXY, YZ and YuW. LHZ drafted the manuscript. HXY, YZ, YuW, XZ, TL, QY and YaW critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. The corresponding author attests that all the listed authors meet authorship criteria and that no others meeting the criteria have been omitted. YaW is the guarantor of the paper.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The UK Biobank received ethics approval from the North West Multicenter Research Ethics Committee (reference number 11/NW/03820). This research has been conducted using the UK Biobank Resource under project number 45676. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data set: Available from the UK Biobank on request (www.ukbiobank. ac. uk). Study protocol and statistical code: Available on request via email from the corresponding author.

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Concordância com as orientações para a realização atempada de imagiologia torácica após novas apresentações de dispneia ou hemoptise em cuidados primários: um estudo de coorte retrospetivo

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RESUMO

Contexto As orientações recomendam a realização urgente de uma radiografia do tórax em caso de apresentação recente de dispneia ou hemoptise, mas existem poucas evidências sobre a sua implementação.

Métodos Analisámos os dados interligados dos cuidados primários e dos exames imagiológicos hospitalares relativos a doentes com mais de 30 anos que se apresentaram recentemente com dispneia ou hemoptise nos cuidados primários entre abril de 2012 e março de 2017. Examinámos a gestão de acordo com as orientações, definida como uma radiografia/ TC do tórax prescrita por um médico de clínica geral realizada no prazo de 2 semanas após a apresentação sintomática, e a variação por características sociodemográficas e antecedentes médicos relevantes utilizando regressão logística. Adicionalmente, entre os doentes diagnosticados com cancro, descrevemos o tempo até ao diagnóstico, a via de diagnóstico e o estádio no momento do diagnóstico por estado de concordância com as orientações.

Resultados No total, 22 560/162 161 (13,9%) doentes com dispneia e 4022/8120 (49,5%) doentes com hemoptise receberam imagiologia de acordo com as orientações dentro do período recomendado de 2 semanas. Os doentes com imagiologia torácica recente prévia à apresentação apresentaram uma probabilidade muito menor de receber imagiologia (OR ajustado 0,16, IC 95% 0,14-0,18 para dispneia e OR ajustado 0,09, IC 95% 0,06-0,11 para hemoptise). Antecedentes de doença pulmonar obstrutiva crónica/asma também foram associados a menores probabilidades de concordância com as orientações (dispneia: OR 0,234, IC 95% 0,225-0,242 e hemoptise: 0,88, 0,79-0,97). A concordância com as orientações foi menor nos casos de dispneia com insuficiência cardíaca prévia, nos fumadores atuais ou ex-fumadores e nos grupos socioeconomicamente mais desfavorecidos. A probabilidade de diagnóstico de cancro do pulmão no prazo de 12 meses foi mais elevada no grupo com imagiologia de acordo com as orientações (dispneia: 1,1% vs. 0,6%; hemoptise: 3,5% vs. 2,7%).

Conclusão A probabilidade de realização de exames imagiológicos urgentes está de acordo com o risco de diagnóstico de cancro subsequente. No entanto, uma grande percentagem de pessoas que apresentam dispneia e hemoptise não recebe imagiologia torácica urgente apesar de ser elegível, o que indica oportunidades para um diagnóstico mais precoce do cancro do pulmão.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Guidelines recommend prompt investigation of dyspnoea and haemoptysis in order to support early diagnosis of lung cancer but there is currently little evidence regarding how these guidelines are implemented.

WHAT THIS STUDY ADDS

- Substantial proportions of patients newly presenting with dyspnoea or haemoptysis did not receive prompt imaging as recommended by clinical guidelines.
- Guideline-concordant imaging was more likely in those later diagnosed with cancer, and less likely in patients who had recently had chest imaging and those with existing respiratory morbidities.
- Among dyspnoea presenters, those with prior heart failure; current or ex-smokers; and those in more socioeconomically disadvantaged groups were also less likely to have guideline-concordant imaging.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Guideline-concordant imaging patterns are suggestive of appropriate clinical reasoning.
- However, certain groups at higher risk of lung cancer were less likely to have urgent imaging.
- Additionally, large proportions of individuals later diagnosed with cancer had not received urgent imaging indicating possible opportunities to improve earlier detection of lung cancer.

INTRODUCTION

International and regional variation in cancer outcomes indicates the need for improvement in lung cancer diagnosis.[1–3] Lung cancer screening for high-risk individuals offers promise,[4–8] but most patients are diagnosed with cancer via symptomatic pathways, typically starting in primary care.[9] Nonetheless, achieving timely diagnosis of symptomatic lung cancer is challenging. The presenting symptoms of lung cancer are often non-specific, and other diagnoses such as chronic obstructive pulmonary disease (COPD), pneumonia and cardiac conditions may offer plausible alternative explanations.

In England and other countries, clinical guidelines have been developed to encourage the recognition and investigation of symptomatic individuals for suspected cancer in primary care.[10–13] The guidelines recommend urgent referral (in England, via the 'two-week wait' fast-track referral pathway) or urgent primary care-led investigation for

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'red-flag' symptoms with relatively high positive predictive value for cancer. For patients presenting with haemoptysis or persistent dyspnoea, urgent chest imaging is recommended.[14 15]

There is currently limited evidence about how primary care referral guidelines for suspected cancer operate in practice. A recent study found that three-fifths of patients with certain alarm symptoms (not including respiratory symptoms) were not referred in spite of guideline recommendations.[16] Understanding guideline implementation could inform the development of quality indicators to improve the diagnostic process.[17] With this goal in mind, we examined the proportion of patients with newly presenting dyspnoea or haemoptysis that received urgent chest imaging concordant with clinical recommendations and related variation by patient-level factors. Additionally, we examined patients diagnosed with cancer in the 12 months following symptomatic presentation by guideline-concordant status.

METHODS

Study design and population

We conducted an observational cohort study using anonymous electronic patient records collected between 1 April 2012 and 15 March 2017. Primary care data from the Clinical Practice Research Datalink (CPRD) GOLD were linked with cancer registration data collated by the National Cancer Registry Analysis Service (NCRAS) and secondary care data, including the English Hospital Episode Statistics Diagnostic Imaging Dataset (HES-DID).

For individuals presenting with haemoptysis or 'unexplained or persistent (longer than 3 weeks)' dyspnoea, the 2005 National Institute for Health and Care Excellence (NICE) guidelines recommend that an urgent chest X-ray is carried out within 2 weeks.[10] We defined two cohorts (each for dyspnoea and haemoptysis) using Read code lists to include individuals aged 30+ years if they had presented with either symptom at least 12 months following practice registration (see online supplemental appendix 1).[18 19] Patients were excluded if their outcome status could not be confirmed, namely if they presented on or after[16] March 2017 (ie, within 2 weeks from the last reliable date in the available DID data); had left their CPRD practice or had died within 2 weeks of presentation; or if their practice had left CPRD within 2 weeks from their presentation.

It was not possible to distinguish between patients who had experienced dyspnoea for 3 weeks or longer before consulting, and those consulting for new-onset dyspnoea as information on symptom duration was not available. Therefore, the first recorded occurrence in primary care was assumed to represent the first presentation of dyspnoea or haemoptysis, respectively.

Outcome of interest

A guideline-concordant imaging event was defined by applying the following three criteria to the linked DID data (see online supplemental appendix 2 for further details):

1. Imaging modality and body region: A chest X-ray or CT scan of the lung or chest using previously published National Interim Clinical Imaging Procedure (NICIP) and Systematised NOmenclature of MEDicine (SNOMED) code lists for such imaging investigations.[20]
2. Source of imaging referral: Imaging events ordered by a General Practitioner (GP) and/or from primary care.
3. Time from symptomatic presentation: Chest imaging that took place 0–14 days following symptomatic presentation was assumed to be relevant to the symptom.

Covariates of interest

Sex (male or female) and age group (10-year age bands from 30 to 39 years to 80+ years) were based on information in CPRD, and socioeconomic status (Index of Multiple Deprivation 2015 score quintiles based on patient postcode of residence) from linked national data. Ethnicity was categorised using information in the order of preference from HES inpatient, HES outpatient and HES-DID files and categorised as white, non-white or missing.

Cancer diagnoses recorded in the 12 months following symptomatic presentation were based on national cancer registration data. Individuals were categorised as having been diagnosed with lung cancer; non-lung cancer excluding non-melanoma skin cancers (C44) and non-malignant tumours (D-code and in situ tumours); or no cancer. For patients with multiple tumours with the same diagnosis date, lung cancers and tumours with non-missing stage were prioritised over non-lung cancers and tumours with missing stage, respectively.

Each individual was categorised as a non-smoker, ex-smoker or current smoker based on primary care records prior to the date of symptomatic presentation by collating previously published Read code lists for smoking status and smoking cessation product codes and using the last observation carried forward approach to impute values closest to the index date where possible.[21–25]

Certain pre-existing conditions could serve as alternative explanations of dyspnoea presentation (COPD or asthma, and heart failure) and haemoptysis, thereby influencing the likelihood of receiving guideline-concordant imaging. Therefore, diagnoses of respiratory disease and heart failure recorded in primary care between 78 and 6 months prior to symptomatic presentation were used to categorise patients as having no morbidities; respiratory conditions only; heart failure only; respiratory conditions or heart failure; and both respiratory conditions and heart failure.[23 26]

Finally, we examined recent prior imaging as another possible explanation for guideline discordance, defined as receipt of primary care-ordered chest imaging up to 6 weeks prior to symptomatic presentation (specifically during a period from −42 days to −1 day from the index date).

Statistical analyses

The two patient-based symptom cohorts were examined independently of each other. Descriptive statistics followed by crude and adjusted logistic regression models were used to examine variation in guideline-concordant imaging by patient-level covariates (sex, age group, ethnicity, smoking status and pre-existing respiratory disease and heart failure). We considered two adjusted models: the first excluded cancer diagnosis status (as this is not known at the time of presentation when decision-making for using imaging takes place), while the second included cancer diagnosis as a covariate (as while this occurs after presentation, it may act as a marker of other unmeasured characteristics of individuals with lung cancer, eg, symptom severity and other features that may have been present at presentation and taken into account by the primary care physician).

Subsequently, among the subgroups of patients in each cohort who were diagnosed with lung cancer, descriptive statistics were used to compare stage at diagnosis (tumour, node, metastases (TNM) stages 1/2, 3/4 or missing), route to diagnosis (one of eight routes as established by NCRAS[27]) and time from symptomatic presentation to diagnosis (the diagnostic interval[28]) by imaging status, using χ^2 tests for significance.

Supplementary analyses

We undertook the following supplementary analyses, which are reported in the online supplemental appendix:

- Considering an imaging interval of 0–28 days from symptomatic presentation (instead of 14 days, as in the main analysis) (online supplemental appendix 3).
- Considering imaging ordered from any source within 14 days of symptomatic presentation (instead of just primary care-ordered imaging, as in the main analysis) (online supplemental appendix 4).

RESULTS

Study population

A total of 162 161 individuals with newly presenting dyspnoea and 8120 individuals with newly presenting haemoptysis were included (table 1). The majority of individuals in both symptom cohorts were 60 years or older, white and either ex-smokers or current smokers as opposed to non-smokers.

Guideline-concordant imaging

A total of 22 560/162 161 (13.9%) patients with dyspnoea and 4022/8120 (49.5%) patients with haemoptysis received guideline-concordant imaging, namely primary care-ordered chest imaging within 2 weeks of presentation (tables 2 and 3).

Among both cohorts, women, the youngest age groups (30–39 and 40–49 year-olds) and those with missing ethnicity were less likely to receive guideline-concordant imaging compared with men, 50–59 year-olds and white individuals, respectively. Individuals who had had chest imaging in the 6 weeks prior to symptomatic presentation were much less likely to receive guideline-concordant imaging (adjusted OR (aOR) 0.16, 95% CI 0.14–0.18 in dyspnoea cohort; aOR 0.09, 95% CI 0.06–0.11 in haemoptysis cohort). History of COPD/asthma was also associated with much lower odds of guideline concordance in dyspnoea presenters (aOR 0.23, 95% CI 0.23–0.24) with a much weaker though similar in direction association among haemoptysis presenters (0.88, 0.79–0.97).

In the dyspnoea cohort, individuals with lower socioeconomic status, current/ex-smokers and individuals with morbidities were less likely to receive imaging. Individuals with pre-existing COPD/asthma or heart failure were much less likely to receive imaging for dyspnoea, with the lowest odds of imaging seen among patients with both morbidity types (0.20, 0.17–0.24).

Adjustment for cancer made no material difference to the associations between sociodemographic variables and guideline-concordant imaging. Individuals who were diagnosed with lung cancer in the year post-presentation were more likely to have received urgent imaging for newly presenting dyspnoea or haemoptysis (2.07, 1.78–2.41 and 1.39, 1.06–1.83, respectively). A similar association was also observed among patients later diagnosed with other cancer types following a dyspnoea presentation (1.33, 1.20–1.48), but without such evidence for haemoptysis.

Lung cancer outcomes by imaging status

The proportion of patients subsequently diagnosed with lung cancer among those who received guideline-concordant imaging was twice as high compared with those not promptly imaged (1.1% vs 0.6%, p<0.001) for dyspnoea presenters, and a third higher for haemoptysis presenters (3.6% vs 2.7%, p=0.076) (table 4). However, the majority (854/1103, 70%) of dyspnoea presenters and (110/253, 43%) of haemoptysis presenters subsequently diagnosed with lung cancer did not receive guideline-concordant imaging.

Compared with those who did not receive guideline-concordant imaging, a slightly higher proportion of those who received imaging were diagnosed with advanced stage (TNM stages III–IV) among both dyspnoea and haemoptysis cohorts though this may have been a chance finding (table 5). There was substantial variation in diagnostic route. Patients who received guideline-concordant imaging following dyspnoea or haemoptysis presentation were more likely to have been diagnosed via the two-week wait pathway for suspected cancer (43% vs 27% for dyspnoea; 59% vs 35% for haemoptysis), and less likely to be diagnosed via an emergency compared with those who did not receive guideline-concordant imaging, particularly for haemoptysis presenters (30% vs 38% for dyspnoea; 9% vs 30% for haemoptysis; p<0.001 for overall variation by concordant imaging status by diagnostic routes in both cohorts, table 5).

Diagnostic interval among patients with lung cancer

Patients with dyspnoea who were subsequently diagnosed with lung cancer had a median (IQR) diagnostic interval of 83 (28–205) days, while among patients with haemoptysis this was 39 (21–71) days. Patients who received imaging following dyspnoea presentation had a shorter diagnostic interval than those who did not (median: 34 vs 114 days, nearly a fourfold difference). In comparison, there was little difference in the distribution of time to cancer diagnosis by imaging status in the smaller haemoptysis cohort (median: 39 days for both groups) (figure 1).

Table 1 Composition of the dyspnoea cohort (n=162 161) and haemoptysis cohort (n=8120)

	Dyspnoea N (%)	Haemoptysis N (%)	P value*
Total	162 161 (100)	8120 (100)	
Sex			
Men	75 683 (47)	4728 (58)	<0.001
Women	86 478 (53)	3392 (42)	
Age group (years)			
30–39	9549 (6)	904 (11)	<0.001
40–49	16 602 (10)	1218 (15)	
50–59	24 772 (15)	1477 (18)	
60–69	38 835 (24)	1768 (22)	
70–79	40 491 (25)	1646 (20)	
80+	31 912 (20)	1107 (14)	
Ethnicity			
White	143 726 (89)	6857 (84)	<0.001
Non-white	7822 (5)	746 (9)	
Missing	10 613 (7)	517 (6)	
IMD quintile			
1 (least deprived)	32 621 (20)	1592 (20)	0.081
2	33 848 (21)	1614 (20)	
3	33 628 (21)	1704 (21)	
4	31 480 (19)	1619 (20)	
5 (most deprived)	30 514 (19)	1588 (20)	
Smoking status			
Non-smoker	34 576 (21)	1955 (24)	<0.001
Ex-smoker	69 667 (43)	3121 (38)	
Current smoker	57 559 (35)	3024 (37)	
Missing	359 (0.2)	20 (0.2)	
Morbidities†			
No COPD/asthma or HF	86 129 (53)	5596 (69)	<0.001
HF only	3417 (2)	144 (2)	
COPD/asthma only	70 008 (43)	2281 (28)	
COPD/asthma and HF	2607 (2)	99 (1)	
Imaging in the 6 weeks prior to presentation			
No prior imaging	153 538 (95)	7567 (93)	<0.001
Prior imaging	8623 (5)	553 (7)	
Cancer diagnosis in the year following symptomatic presentation			
No	158 575 (98)	7742 (95)	<0.001
Yes (lung cancer)	1103 (1)	253 (3)	
Yes (other cancer)	2483 (2)	125 (2)	

*From χ^2 test.
†Recorded in a period from 6 to 78 months prior to symptomatic presentation. Respiratory disease=COPD/asthma.
COPD, chronic obstructive pulmonary disease; HF, heart failure; IMD, Index of Multiple Deprivation.

Supplementary analyses

Additional analyses considering a 4-week interval in which imaging took place (online supplemental appendix 3), or imaging ordered from secondary care and other sources in addition to imaging ordered by GPs (online supplemental appendix 4) identified a greater number of patients who received guideline-concordant imaging but patterns of variation by patient factors remained largely unchanged. One exception was in the haemoptysis cohort, where current smokers and patients subsequently diagnosed with lung

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Table 2 Receipt of guideline-concordant imaging within 2 weeks from presentation among patients with newly presenting dyspnoea (n=162 161)

Dyspnoea	Total	Guideline-concordant imaging n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Total	162 161	22 560 (14)	–	–	–
Sex			*<0.001*	*<0.001*	*<0.001*
Men	75 683	10 842 (14)	Ref	Ref	Ref
Women	86 478	11 718 (14)	**0.94 (0.91 to 0.96)**	**0.93 (0.90 to 0.95)**	**0.93 (0.90 to 0.96)**
Age group (years)			*<0.001*	*<0.001*	*<0.001*
30–39	9549	904 (9)	**0.65 (0.61 to 0.71)**	**0.55 (0.51 to 0.60)**	**0.55 (0.51 to 0.60)**
40–49	16 602	2216 (13)	0.96 (0.91 to 1.02)	**0.88 (0.83 to 0.93)**	**0.88 (0.83 to 0.93)**
50–59	24 772	3413 (14)	Ref	Ref	Ref
60–69	38 835	5462 (14)	1.02 (0.98 to 1.07)	**1.10 (1.04 to 1.15)**	**1.09 (1.04 to 1.14)**
70–79	40 491	6084 (15)	**1.11 (1.06 to 1.16)**	**1.14 (1.09 to 1.19)**	**1.13 (1.08 to 1.18)**
80+	31 912	4481 (14)	1.02 (0.97 to 1.07)	**0.93 (0.88 to 0.98)**	**0.92 (0.87 to 0.97)**
Ethnicity			*<0.001*	*<0.001*	*<0.001*
White	143 726	20 297 (14)	Ref	Ref	Ref
Non-white	7822	1139 (15)	1.04 (0.97 to 1.11)	0.96 (0.90 to 1.03)	0.97 (0.90 to 1.04)
Missing	10 613	1124 (11)	**0.72 (0.68 to 0.77)**	**0.68 (0.64 to 0.73)**	**0.68 (0.64 to 0.73)**
IMD quintile			*<0.001*	*0.001*	*0.001*
1 (least deprived)	32 621	5052 (15)	Ref	Ref	Ref
2	33 848	4754 (14)	**0.89 (0.85 to 0.93)**	**0.93 (0.89 to 0.97)**	**0.93 (0.89 to 0.97)**
3	33 628	4816 (14)	**0.91 (0.87 to 0.95)**	0.97 (0.93 to 1.01)	0.97 (0.93 to 1.01)
4	31 480	4173 (13)	**0.83 (0.80 to 0.87)**	**0.94 (0.90 to 0.98)**	**0.94 (0.90 to 0.98)**
5 (most deprived)	30 514	3752 (12)	**0.77 (0.73 to 0.80)**	**0.91 (0.87 to 0.96)**	**0.91 (0.87 to 0.95)**
Smoking status			*<0.001*	*<0.001*	*<0.001*
Non-smoker	34 576	5817 (17)	Ref	Ref	Ref
Ex-smoker	69 667	9483 (14)	**0.78 (0.75 to 0.81)**	**0.94 (0.91 to 0.98)**	**0.94 (0.90 to 0.98)**
Current smoker	57 559	7215 (13)	**0.71 (0.68 to 0.74)**	**0.88 (0.85 to 0.92)**	**0.88 (0.84 to 0.91)**
Missing	359	45 (13)	**0.71 (0.52 to 0.97)**	**0.63 (0.46 to 0.86)**	**0.62 (0.45 to 0.85)**
Morbidities‡			*<0.001*	*<0.001*	*<0.001*
No COPD/asthma or HF	86 129	17 678 (21)	Ref	Ref	Ref
HF only	3417	502 (15)	**0.67 (0.61 to 0.73)**	**0.61 (0.55 to 0.67)**	**0.61 (0.55 to 0.67)**
COPD/asthma only	70 008	4235 (6)	**0.25 (0.24 to 0.26)**	**0.23 (0.23 to 0.24)**	**0.23 (0.23 to 0.24)**
COPD/asthma and HF	2607	145 (6)	**0.23 (0.19 to 0.27)**	**0.20 (0.17 to 0.24)**	**0.20 (0.17 to 0.24)**
Imaging in the 6 weeks prior to presentation			*<0.001*	*<0.001*	*<0.001*
No prior imaging	153 538	22 271 (15)	Ref	Ref	Ref
Prior imaging	8623	289 (3)	**0.20 (0.18 to 0.23)**	**0.16 (0.14 to 0.18)**	**0.16 (0.14 to 0.18)**
Cancer diagnosis in the year following symptomatic presentation			*<0.001*		*<0.001*
No cancer	158 575	21 840 (14)	Ref	–	Ref
Lung cancer	1103	249 (23)	**1.83 (1.58 to 2.10)**	**–**	**2.07 (1.78 to 2.41)**
Other cancer	2483	471 (19)	**1.47 (1.32 to 1.62)**	**–**	**1.33 (1.20 to 1.48)**

Joint testing p values are presented in italics.
Cell values are provided in bold when accompanying 95% confidence interval values exclude parity (1.0).
*Adjusting for sex, age, ethnicity, IMD quintile, smoking status, morbidities and prior imaging.
†Adjusting for sex, age, ethnicity, IMD quintile, smoking status, morbidities, prior imaging and cancer diagnosis.
‡Recorded in the 78 months to 6 months prior to symptomatic presentation.
COPD, chronic obstructive pulmonary disease; HF, heart failure; IMD, Index of Multiple Deprivation

cancer were more likely to have receive prompt imaging (whereas there was no such evidence in the main analysis).

DISCUSSION

Summary of findings

Less than one in seven patients with newly presenting dyspnoea and one in two patients with newly presenting haemoptysis received primary care-ordered chest imaging within 2 weeks of presentation in line with national guidelines. Women, younger patients, individuals who had received chest imaging before presentation and those with pre-existing COPD or asthma were less likely to receive guideline-concordant imaging, while individuals diagnosed with lung cancer in the year following presentation were more likely to have been promptly imaged. Of those who subsequently received a lung cancer diagnosis, most patients presenting with dyspnoea (854/1103, 70%) and many patients presenting with haemoptysis (110/253, 43%) had not received timely imaging.

Table 3 Receipt of guideline-concordant imaging within 2 weeks from presentation among patients with haemoptysis (n=8120)

Haemoptysis	Total	Guideline-concordant imaging n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Total	8120	4022 (50)	–	–	–
Sex			*0.007*	*0.001*	*0.001*
Men	4728	2402 (51)	Ref	Ref	Ref
Women	3392	1620 (48)	**0.89 (0.81 to 0.97)**	**0.85 (0.77 to 0.93)**	**0.85 (0.77 to 0.93)**
Age group (years)			*<0.001*	*<0.001*	*<0.001*
30–39	904	369 (41)	**0.69 (0.58 to 0.81)**	**0.65 (0.55 to 0.77)**	**0.66 (0.55 to 0.78)**
40–49	1218	566 (46)	0.86 (0.74 to 1.01)	**0.84 (0.72 to 0.98)**	**0.84 (0.72 to 0.98)**
50–59	1477	740 (50)	Ref	Ref	Ref
60–69	1768	979 (55)	**1.24 (1.08 to 1.42)**	**1.28 (1.11 to 1.48)**	**1.27 (1.10 to 1.47)**
70–79	1646	856 (52)	1.08 (0.94 to 1.24)	1.15 (0.99 to 1.34)	1.14 (0.98 to 1.32)
80+	1107	512 (46)	0.86 (0.73 to 1.00)	0.89 (0.75 to 1.05)	0.88 (0.74 to 1.04)
Ethnicity			*0.001*	*<0.001*	*<0.001*
White	6857	3438 (50)	Ref	Ref	Ref
Non-white	746	369 (49)	0.97 (0.84 to 1.13)	1.04 (0.88 to 1.22)	1.04 (0.89 to 1.22)
Missing	517	215 (42)	**0.71 (0.59 to 0.85)**	**0.69 (0.57 to 0.83)**	**0.69 (0.58 to 0.84)**
IMD quintile			*0.416*	*0.157*	*0.171*
1 (least deprived)	1592	789 (50)	Ref	Ref	Ref
2	1614	797 (49)	0.99 (0.86 to 1.14)	0.99 (0.86 to 1.14)	0.99 (0.86 to 1.14)
3	1704	855 (50)	1.02 (0.89 to 1.18)	1.02 (0.89 to 1.18)	1.02 (0.89 to 1.18)
4	1619	771 (48)	0.93 (0.81 to 1.06)	0.90 (0.78 to 1.04)	0.90 (0.78 to 1.04)
5 (most deprived)	1588	809 (51)	1.06 (0.92 to 1.21)	1.08 (0.94 to 1.26)	1.08 (0.93 to 1.25)
Smoking status			*0.760*	*0.426*	*0.432*
Non-smoker	1955	951 (49)	Ref	Ref	Ref
Ex-smoker	3121	1547 (50)	1.04 (0.93 to 1.16)	0.98 (0.86 to 1.10)	0.97 (0.86 to 1.10)
Current smoker	3024	1515 (50)	1.06 (0.95 to 1.19)	1.06 (0.94 to 1.19)	1.05 (0.93 to 1.19)
Missing	20	9 (45)	0.86 (0.36 to 2.09)	0.75 (0.30 to 1.84)	0.75 (0.31 to 1.85)
Morbidities‡			*0.182*	*0.065*	*0.063*
No COPD/asthma or HF	5596	2799 (50)	Ref	Ref	Ref
HF only	144	80 (56)	1.25 (0.90 to 1.74)	1.13 (0.80 to 1.60)	1.14 (0.81 to 1.62)
COPD/asthma only	2281	1094 (48)	0.92 (0.84 to 1.02)	**0.88 (0.79 to 0.97)**	**0.88 (0.79 to 0.97)**
COPD/asthma and HF	99	49 (49)	0.98 (0.66 to 1.46)	0.86 (0.57 to 1.30)	0.87 (0.58 to 1.31)
Imaging in the 6 weeks prior to presentation			*<0.001*	*<0.001*	*<0.001*
No prior imaging	7567	3971 (52)	Ref	Ref	Ref
Prior imaging	553	51 (9)	**0.09 (0.07 to 0.12)**	**0.09 (0.06 to 0.12)**	**0.09 (0.06 to 0.11)**
Cancer diagnosis in the year following symptomatic presentation			*0.077*		*0.057*
No cancer	7742	3816 (49)	Ref	–	Ref
Lung cancer	253	143 (57)	**1.34 (1.04 to 1.72)**	**–**	**1.39 (1.06 to 1.83)**
Other cancer	125	63 (50)	1.05 (0.73 to 1.49)	–	1.05 (0.72 to 1.52)

Joint testing p values are presented in italics.
Cell values are provided in bold when accompanying 95% confidence interval values exclude parity (1.0).
*Adjusting for sex, age, ethnicity, IMD quintile, smoking status, morbidities and prior imaging.
†Adjusting for sex, age, ethnicity, IMD quintile, smoking status, morbidities, prior imaging and cancer diagnosis.
‡Recorded in the 78 months to 6 months prior to symptomatic presentation.
COPD, chronic obstructive pulmonary disease; HF, heart failure; IMD, Index of Multiple Deprivation

In both cohorts, those who did not receive prompt imaging before lung cancer diagnosis were more likely to be diagnosed as emergencies. Among patients with lung cancer initially presenting with dyspnoea, prompt imaging was associated with shorter intervals to diagnosis.

Comparison with prior literature

A study examining urgent primary care referrals for six 'red-flag' cancer symptoms found that only 40% of eligible patients received an urgent referral within 14 days of presentation, with substantial variation by symptom[16]; in our study, the corresponding figures for prompt chest imaging being 14% and 50% for dyspnoea and haemoptysis, respectively. The proportion of symptomatic patients who were subsequently diagnosed with cancer without having received an urgent or fast-track referral ranged from 2.8% to 9.5% by symptom; in comparison, we found the respective proportions for lung cancer to be 0.6% of dyspnoea presenters and 2.7% of haemoptysis presenters. Our results are also aligned to a US study that identified 38% of patients with lung cancer had had a missed opportunity,[29] and a study using English electronic health records

Cancro do pulmão

Table 4 Cancer diagnoses in the year following symptomatic presentation by imaging status

	Dyspnoea		Haemoptysis	
	No guideline-concordant imaging within 2 weeks from presentation	Guideline-concordant imaging within 2 weeks from presentation	No guideline-concordant imaging within 2 weeks from presentation	Guideline-concordant imaging within 2 weeks from presentation
Total (%)	139 601 (86)	22 560 (14)	4098 (50)	4022 (50)
No cancer (%)	136 735 (98)	21 840 (97)	3926 (96)	3816 (95)
Lung cancer (%)	854 (0.6)	249 (1.1)	110 (2.7)	143 (3.6)
Non-lung cancer (%)	2012 (1.4)	471 (2.1)	62 (1.5)	63 (1.6)
P value*	<0.001		0.076	

*X^2 test.

data that found 65% of patients with lung cancer who had a chest X-ray had received it 2 weeks or longer after presentation.[30]

Our findings indicate that patients with lung cancer who received guideline-concordant imaging had shorter diagnostic intervals but a higher proportion were diagnosed with advanced stage; this concords with previous research on patient populations with lung cancer that reported shorter diagnostic intervals among those with late-stage versus early-stage cancer.[31 32] This may also reflect confounding by indication and the waiting time paradox which has been previously described.[33]

Strengths and limitations

We analysed nationally representative linked primary care data. The HES-DID and NCRAS data sets represent gold standard sources of information on ascertaining imaging investigations[34] and cancer diagnoses,[35] respectively.

We acknowledge several limitations. First, factors beyond clinical decision-making in primary care such as imaging capacity and patients' ability to attend for the ordered investigations may have influenced whether or not guideline-concordant imaging occurred. Nevertheless, when we examined a longer period for the imaging to occur (online supplemental appendix 3) or included imaging ordered by other sources (online supplemental appendix 4), there remained substantial numbers of eligible individuals who did not receive prompt imaging. Furthermore, CT imaging may be subject to longer waiting times due to capacity constraints in comparison to X-rays. However, the vast majority (99%) of imaging events conducted in the chest region in both symptom cohorts (within 2 weeks from presentation or with no time constraint) were chest X-rays not CT imaging (data not shown).

The 2005 NICE guidelines indicate that patients with persistent dyspnoea should be ordered urgent chest imaging, defined as lasting 3 weeks or more.10 Some of the individuals in our dyspnoea cohort may have presented with dyspnoea less than 3 weeks after onset, leading to the underestimation of the true proportion of clinically eligible individuals receiving guideline-concordant imaging. Free text primary care records data could have captured this kind of detail, but are not available for research purposes due to resource constraints in ensuring non-disclosivity of the data.[36]

We assumed that the chest imaging events identified following presentation were related and not incidental to the dyspnoea or haemoptysis, which could have led to the overestimation of guideline concordance. Similarly, we examined lung cancers that were diagnosed in the 12 months following symptomatic presentation: some of these cancers could also have been unrelated to the coded symptom. However, most imaging was conducted within the first 1–2 days from presentation, and the majority of lung cancers diagnosed in the 12 months after presentation were identified in the first 6 months (71% and 93% for dyspnoea and haemoptysis, respectively), supporting the validity of our assumptions (data not shown).

Implications

Individuals who presented with dyspnoea or haemoptysis and were later diagnosed with lung cancer were more likely to have received guideline-concordant imaging than symptomatic individuals who were not diagnosed with lung cancer. This suggests appropriate clinical decision-making took place for these individuals, though we must acknowledge there are additional patient, doctor and system-level factors contributing to urgent imaging taking place following presentation.

Some of the observed variation in guideline-concordant imaging may have a plausible explanation. Individuals with pre-existing respiratory disease and/or heart failure were less likely to receive urgent imaging, possibly because the symptoms were attributed to those conditions.[37] Women, younger patients and those who had had imaging prior to presentation were also less likely to receive guideline-concordant care, which may reflect appropriate assessment of the lower prior risk of lung cancer in these groups (compared with men, older patients and individuals who had not been ordered chest imaging recently, respectively).

Nevertheless, other patterns of variation are harder to explain: current or ex-smokers and patients residing in poorer neighbourhoods were less likely to receive prompt imaging for dyspnoea despite being at relatively higher risk of lung cancer compared with non-smokers or more affluent patients.[38] These associations require further elucidation, including through qualitative studies.

Substantial proportions of the individuals later diagnosed with cancer did not receive guideline-concordant imaging, potentially representing missed opportunities for earlier lung cancer diagnosis. Clinical case note review could enhance our understanding of the reasons for guideline discordance and missed opportunities.[39,40] Nevertheless, the findings demonstrate the potential for investigation or referral activity captured in electronic health record systems to be used as a diagnostic quality indicator. Additionally, examining provider-level variability in guideline-concordant care could be informative,[41] noting that guideline concordance increased when we examined imaging ordered by all sources and not just primary care.

A critical consideration prior to improving guideline adherence is imaging access and capacity. Chest X-rays may miss 20% of symptomatic lung cancers[42] while CT capacity has been insufficient in England since before the emergence of COVID-19.[43] The recently launched community diagnostic centres (aiming to improve access to diagnostic tests outside of hospital settings) could form part of service redesigns aimed at improving lung cancer diagnosis pathways.[44]

Table 5 Lung cancer-related outcomes by imaging status

	Patients with dyspnoea diagnosed with lung cancer (N=1103)		Patients with haemoptysis diagnosed with lung cancer (N=253)	
	No guideline-concordant imaging	Guideline-concordant imaging	No guideline-concordant imaging	Guideline-concordant imaging
Total, N (%)	854 (77)	249 (23)	110 (43)	143 (57)
Stage at diagnosis	P=0.116*		P=0.673*	
Stages I–II (%)	161 (19)	38 (15)	24 (22)	29 (20)
Stages III–IV (%)	561 (66)	181 (73)	71 (65)	99 (69)
Stage missing (%)	132 (15)	30 (12)	15 (14)	15 (10)
Route to diagnosis	P<0.001*		P<0.001*	
TWW (%)	232 (27)	106 (43)	38 (35)	84 (59)
General Practitioner referral (%)	160 (19)	47 (19)	25 (23)	33 (23)
Emergency (%)	323 (38)	75 (30)	33 (30)	13 (9)
Hospital (%)	124 (15)	18 (7)	12 (11)	11 (8)
DCO/unknown (%)	15 (2)	3 (1)	2 (2)	2 (1)

*X^2 test p value.
DCO, death certificate only; TWW, two-week wait (fast-track referral pathway for suspected cancer)[27] .

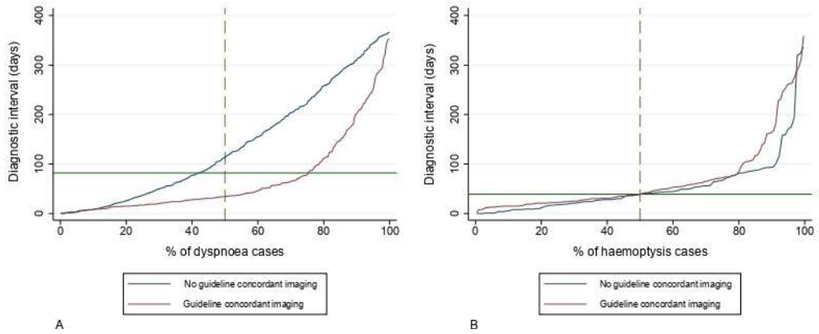

Figure 1 Time from symptomatic presentation to lung cancer diagnosis by imaging status in 1103 patients with dyspnoea (A) and 253 patients with haemoptysis (B). The horizontal green line represents the median diagnostic interval in all patients with lung cancer in the dyspnoea cohort (83 days) and the haemoptysis cohort (39 days), respectively.

CONCLUSION

In the context of cancer diagnosis, primary care-ordered urgent imaging patterns broadly accord with clinical risk. However, large proportions of dyspnoea or haemoptysis presenters do not receive prompt imaging, likely representing missed opportunities for more timely lung cancer diagnosis, especially in patients with haemoptysis. Developing quality metrics based on guideline concordance for prompt chest imaging could improve the quality and equity of urgent imaging in primary care.

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Nem toda a pieira é asma

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Um homem de 41 anos, previamente diagnosticado com asma, apresentou uma doença semelhante a gripe e falta de ar. Foi tratado para COVID-19 moderada a grave e exacerbação da asma. A angiografia pulmonar por TC (APTC) revelou infiltrados foscos peribroncovasculares assimétricos consistentes com a COVID-19 e espessamento da parede brônquica principal direita com material de alta densidade que se pensa ser consistente com impactação mucosa (figura 1A). Recebeu alta 8 dias após a admissão.

Na revisão após 4 meses, relatou falta de ar contínua e tosse com expetoração verde. Os testes de função pulmonar revelaram um volume expiratório forçado em 1 segundo (FEV_1) de 2,4 L (67% do previsto), capacidade vital forçada (FVC) de 4,2 L (97%), rácio FEV_1/FVC de 0,56 e capacidade de difusão normal dos pulmões para o monóxido de carbono. A fração de óxido nítrico exalado era de 34 ppb.

Oito semanas mais tarde, apesar da terapêutica inalatória otimizada, os sintomas agravaram-se e o doente desenvolveu hemoptise. A APTC mostrou progressão do espessamento da parede brônquica principal direita com obstrução mucosa distal ao material de alta densidade (figura 1B,C).

Na semana seguinte, uma broncoscopia de fibra ótica revelou o aparecimento de um corpo estranho (CE) que atravessava o orifício do lobo superior direito com tecido de granulação circundante. Aparecia parcialmente epitelizado na camada mucosa. Foi difícil extrair o objeto devido a uma resistência significativa e a preocupações com hemorragias e danos nas vias respiratórias.

O procedimento foi terminado e foi administrado um ciclo de 7 dias de antibióticos orais. 14 dias mais tarde, numa broncoscopia rígida sob anestesia geral, foi removido com sucesso um objeto

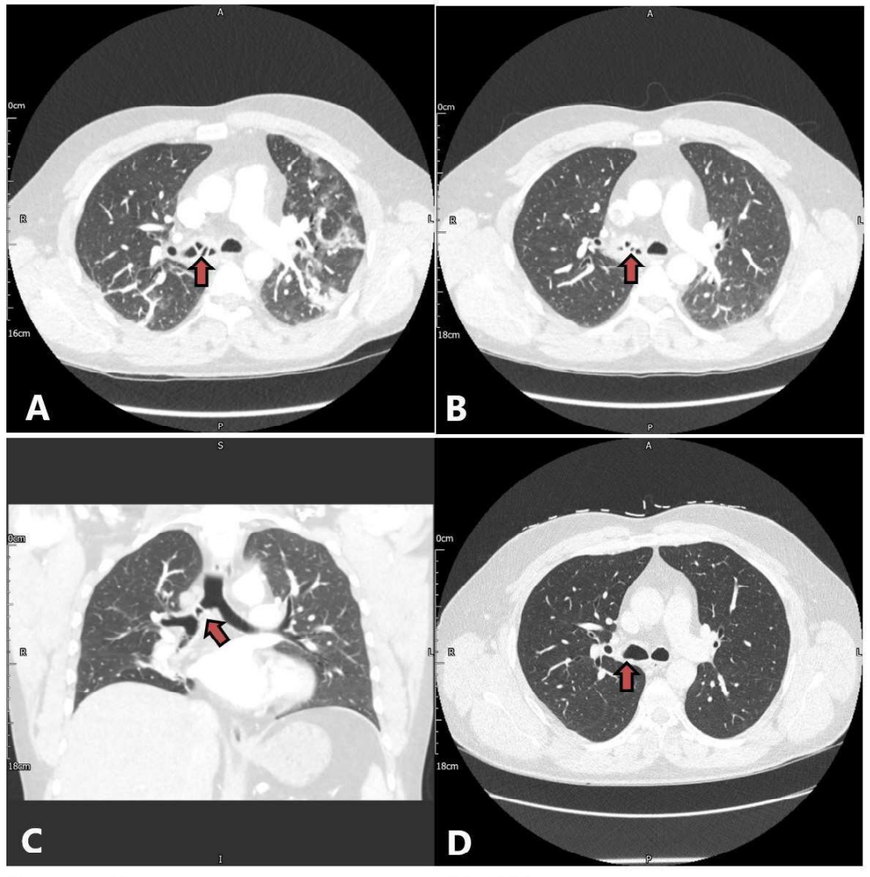

Figura 1 (A) Vista coronal da angiografia pulmonar por TC (APTC) realizada na primeira apresentação aguda de infeção por COVID-19, mostrando o aparecimento de material de alta densidade com septações que se pensa serem consistentes com o aparecimento de impactação mucosa associada a espessamento da parede brônquica no brônquio principal direito (BPD). (B,C) Cortes coronal e axial da APTC realizados na segunda apresentação aguda com hemoptise, mostrando o material de alta densidade e a progressão do espessamento da parede brônquica no BPD. (D) Vista coronal de TC de tórax de dose baixa realizada 6 meses após broncoscopia rígida e extração de corpo estranho, mostrando a resolução das alterações.

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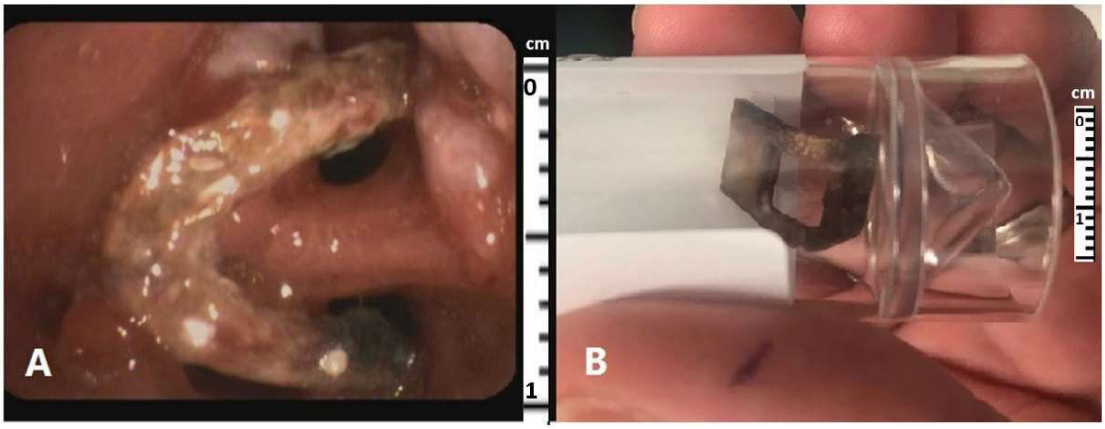

Figura 2 (A) Vista broncoscópica do lobo superior direito RC1 sugerindo o aparecimento de um objeto estranho parcialmente integrado na camada mucosa. (B) O objeto de plástico em forma de L, medindo 1 cm, é visto num pote de amostras após a remoção.

em forma de L com uma pinça montada e hemorragia mínima (figura 2).

Ao rever o material extraído com o doente, este reconheceu-o como um componente de um camião de brincar com o qual brincava aos 9 anos de idade. Posteriormente, desenvolveu sintomas de asma mal controlados durante a adolescência, resistentes ao tratamento de dose elevada para asma. A extração do CE levou à resolução dos sintomas e das alterações radiológicas (figura 1D).

DISCUSSÃO

Apresentamos um caso de remoção de CE mais de três décadas após a aspiração com o consentimento do doente. Até onde sabemos, este é o maior tempo relatado entre aspiração e remoção do CE da via aérea.

Os brinquedos representam 5,8% dos casos de inalação e ingestão de CE em crianças.[1] No entanto, os brinquedos são extremamente raros como CE retidos a longo prazo em adultos. A maioria dos CE são achados alojados na árvore brônquica direita devido ao trajeto mais vertical do brônquio principal direito.[2] A persistência de anomalias neste local deve levantar a suspeita de aspiração de CE quando observada em exames imagiológicos. A ausência de antecedentes de aspiração de CE não deve excluir o diagnóstico.

A obstrução de grandes vias aéreas após a inalação de corpos estranhos, mais comum em pediatria, causa sintomas de dificuldade respiratória imediata, levando a intervenções urgentes.[3] No entanto, os corpos estranhos alojados em vias aéreas mais pequenas levam a uma oclusão incompleta das vias aéreas, o que produz sintomas que imitam a asma crónica, atrasando assim o diagnóstico de inalação de corpos estranhos.[3] Estes sintomas são normalmente ignorados até que um fator desencadeador significativo, no caso do nosso doente, a COVID-19, exacerbe suficientemente a condição para iniciar investigações detalhadas.

O nosso doente relatou sintomas de asma mal controlados com infeções torácicas recorrentes durante a maior parte da sua vida. Foi tratado com uma terapia inalatória crescente e cursos repetidos de antibióticos. Não se recorda de ter sido submetido a TAC ou broncoscopia na sua infância. Com o diagnóstico correto neste caso, poderiam ter sido evitados tratamentos de alta dosagem com potenciais efeitos secundários, um tempo significativo perdido em consultas de saúde e a utilização desnecessária de recursos de saúde. A prática atual defende a avaliação por uma equipa multidisciplinar com investigações adicionais, como a broncoscopia, em crianças com asma mal controlada, apesar da otimização do tratamento.[4]

No nosso caso, foi efetuada uma broncoscopia flexível para determinar o diagnóstico. Em concordância com a literatura, sugerimos a remoção de um CE não identificado, sugestivo de objeto metálico ou cortante, através de broncoscopia rígida, permitindo um maior canal de trabalho para instrumentação e controlo de hemorragia, evitando lesões nas cordas vocais e paredes brônquicas.[2 3]

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