

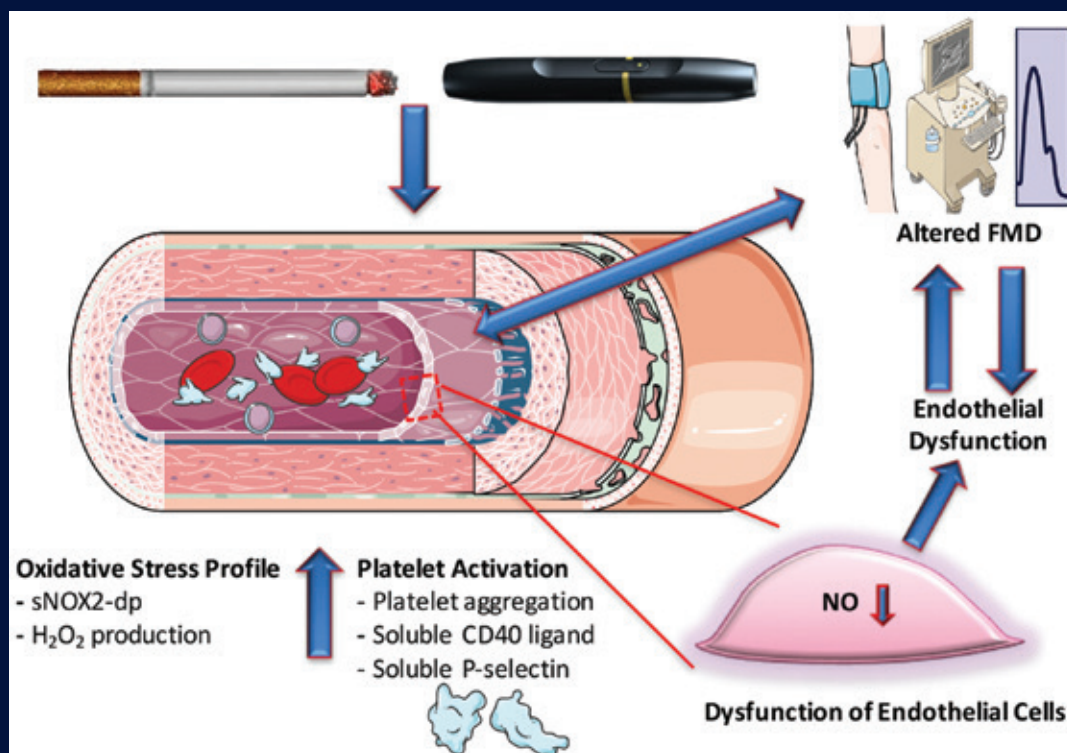
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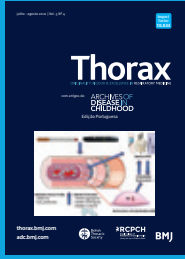
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Rua Bernardo Costa nº127, 1º Esquerdo
2775-809 Carcavelos
Contacto: 938311875
Email: geral@medjournal.pt
www.medjournal.pt
NIF: 510 542 719

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E: info.adc@bmj.com
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Malcolm Smith
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British Thoracic Society

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M: +1 215 933 8484

E: ray.thibodeau@contentednet.com

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E: production.thorax@bmj.com

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Editorial

Neste número da tradução de resumos de artigos das Revistas *Thorax* e *Archives of Disease in Childhood*, dedicados aos Sócios das Sociedades Científicas de Pneumologia, Alergologia e Imunologia Clínica, Medicina Geral e Familiar e Pediatria, os Conselhos Editorial e Científico não foram imunes à literatura avassaladora sobre a pandemia COVID-19.

E nada mais oportuno do que sublinhar a cooperação entre especialidades, que se verificou nas Unidades de Cuidados Intensivos, entre os Médicos Intensivistas de Adultos e os Pediatras. Este Editorial (pag. 151) faz um convite à reflexão. Refletir sobre os modelos de colaboração, os locais onde devem ser efetuados, os recursos a utilizar e mobilizar. E focam-se de forma particular na comunicação e na transparência. Terminam com uma nota sobre a necessidade de refletir sobre o que se passou, para poder planear antecipadamente uma outra situação de catástrofe, qualquer que seja. Sobretudo se nesse caso, adultos e crianças estiverem igualmente envolvidos e não, como neste caso e para a felicidade de todos, as crianças forem poupadas...

Centrado também na cooperação e qualidade em cuidados de saúde está o artigo da pag. 182, “Iniciativas para reduzir os tratamentos da bronquiolite em serviço de urgência e cuidados de saúde primários”. A bronquiolite é uma doença respiratória inferior aguda que atinge as crianças abaixo dos 2 anos de idade maioritariamente abaixo do ano e é a causa mais frequente de internamento neste grupo etário. Por ter causa viral, sobretudo vírus sincicial respiratório (VSR), ocorre por surtos anuais, sazonais, no outono/inverno... ou pelo menos assim aconteceu nos anos anteriores à pandemia covid-19, já que em 2021 têm sido repostados casos associados a VSR em julho. Há mais de 40 anos que é sugerido que não há terapêuticas eficazes na bronquiolite aguda. No entanto assistimos sistematicamente à sua utilização e à publicação de estudos científicos que demonstram a sua inutilidade. Neste caso uma intervenção efetuada nos serviços de urgência hospitalares e nos cuidados de saúde primários demonstrou a redução de utilização destas terapêuticas fúteis... e ainda que os resultados possam ser transitórios, como anteriormente demonstrado, poupam-se recursos que farão falta em outros setores...

E há ainda mais artigos de interesse a explorar. Particularmente relevantes a chamada de atenção para a influencia dos hábitos de vida na saúde respiratória: trabalho por turnos (pag. 153) e tabagismo. E agora mesmo que não sejamos nós a fumar, se as nossas avós fumaram (pag. 168), as consequências recaíram sobre os netos...

E os culpados são sempre os mesmos. Na pag. 189 pode ler-se que os fatores de risco para o desenvolvimento de limitação irreversível dos débitos ventilatórios são asma atual, infeções do trato respiratório infantil, asma e exposição a poluição atmosférica.

Por último, mas não menos relevante, mais um artigo a ler com atenção na pag. 174 e seguintes, o impacto de ter tuberculose (TB), mesmo já na fase tratada, sobre os rendimentos e o emprego em contexto urbano de baixos rendimentos, no Malawi. Numa época em que tanto se fala das desigualdades sociais e económicas e do seu impacto na saúde e na sobrevivência este artigo avança que a atenuação do impacto sócio-económico da tuberculose (TB) é fundamental para a Estratégia de erradicação da TB da OMS.

Não recomendo que levem estas leituras para as férias. Desejo que sejam um período de interregno e novas descobertas. Mas quando voltarem será seguramente uma oportunidade de atualização de conhecimentos na retoma do trabalho que se adivinha continuará desafiante e árduo...

Boas férias!

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Encontrar formas de os médicos pediatras cuidarem das "crianças" grandes e salvarem os adultos numa pandemia

Justin Robison,¹ Kenneth E Remy^{1,2}

A OMS declarou a COVID-19 como uma pandemia em março de 2020. No final de 2020, os Centros de Controle e Prevenção de Doenças dos EUA demonstraram que a taxa cumulativa de hospitalizações associadas à COVID-19 para doentes <18 anos de idade era de 23,9 por 100.000 habitantes em comparação com adultos com 18 ou mais anos de idade a 449,9 por 100.000 habitantes.¹ Uma análise recente realizada pela *Society of Critical Care Medicine* estimou que os EUA tinham 34,7 camas de cuidados críticos por 100.000 habitantes; 5% das quais correspondem a camas de cuidados críticos pediátricos e 24% a camas de cuidados intensivos neonatais.² A consequente escassez de recursos da unidade de cuidados intensivos (UCI) para adultos devido ao surto de infecções COVID-19 despertou o engenho numa época em que o mundo foi mergulhado no caos.

Neste contexto, Sinha *et al*, nesta edição, encontraram formas criativas para os médicos pediatras cuidarem de adultos doentes com a doença COVID-19.³ Numa rubrica cuidadosamente elaborada, os autores mostram como um planeamento cuidadoso e uma implementação metódica em Inglaterra podem mobilizar recursos de emergência em tempo de crise. Como tal, o seu sucesso satisfaz a necessidade de aumentar os recursos das UCI para adultos durante o início da pandemia da COVID-19, ao mesmo tempo que satisfaziam as necessidades de cuidados críticos pediátricos do país. No início da pandemia, um número de médicos especialistas em cuidados críticos de adultos e crianças desenvolveram recomendações sobre como cuidar clinicamente de adultos em ambientes pediátricos.^{4,5} À medida que o desastre mundial prosseguia, começaram a surgir vários modelos para implementar estas recomendações em três modelos diferentes: gestão exclusiva de adultos em UCI pediátricas (UCI pediátrica) com uma UCI pediátrica localizada a nível regional para cuidar de crianças, uma unidade para adultos híbrida e uma UCI pediátrica, ou o estabelecimento de novas UCI

para adultos composta por médicos de cuidados críticos pediátricos (resumido no quadro 1).

Estes modelos foram devidamente implementados por múltiplas instituições em todo o mundo. A experiência de Sinha *et al* em Inglaterra é única devido à magnitude e coordenação dos seus esforços em todo um país. No início da pandemia, a nossa instituição adotou um modelo de médicos de UCI pediátricas que cuidavam de adultos gravemente doentes no nosso hospital pediátrico ao lado de crianças. No entanto, na segunda vaga (Outono de 2020), mobilizámos médicos e enfermeiros de UCI pediátricas para as UCI COVID-19 para adultos em todo o nosso sistema de saúde, uma vez que foram criadas novas UCI de COVID-19 para adultos aquando da identificação de espaços físicos adicionais. A partir destas experiências, pudemos considerar quais os aspetos destes modelos que funcionaram bem e identificar outras oportunidades de crescimento. Enquanto cuidávamos de adultos nas nossas UCI pediátricas, confiámos nos nossos fortes e bem estabelecidos sistemas de comunicação entre membros da nossa equipa familiar para nos adaptarmos a esta nova população de doentes.

No entanto, estávamos perfeitamente cientes de que, caso fossem necessários cuidados específicos para adultos (ou seja, cateterização interventiva), os doentes adultos teriam de ser transportados de volta para o hospital de adultos, o que poderia resultar em atrasos nos cuidados. Na segunda vaga, como os prestadores de cuidados intensivos pediátricos estavam a cobrir as UCI COVID-19 de adultos no hospital de adultos, alguns doentes exigiram uma avaliação urgente para síndrome coronária aguda e acidente vascular cerebral, o que foi facilitado com prestadores de cuidados específicos para adultos - habituados a prestar estas avaliações e intervenções no local onde se sentiam familiarizados.

Porém, este "luxo" de oferecer cuidados no hospital para adultos por prestadores de cuidados pediátricos foi em parte possível devido ao espaço físico disponível. Se fosse atingida capacidade nestes locais, o planeamento de todo o sistema previa o regresso dos doentes que iriam ser atendidos nas UCI pediátricas. Independentemente do modelo de utilização de médicos de cuidados críticos pediátricos para as necessidades de cui-

dados críticos de adultos, existem diferenças fundamentais nos cuidados críticos de adultos e pediátricos, uma vez que as crianças não são "pequenos adultos", nem os adultos crianças "grandes". Reconhecer que os adultos podem ser tratados em ambientes pediátricos ou por médicos pediatras de uma forma diferente da dos adultos e o reconhecimento de lacunas nestes cuidados é fundamental para o sucesso.

Para que os recursos possam ser utilizados com sucesso numa UCI pediátrica convertida para adultos, é necessário, em primeiro lugar, criar um plano estruturado para garantir o sucesso. Esta estrutura deve incluir uma compreensão fundamental (ou reconhecimento de onde existem de facto as lacunas de conhecimento) de potenciais doenças de adultos com complicações, a disponibilidade de serviços de consulta de adultos, a requalificação do pessoal relevante, a capacidade de reorganizar o espaço da UCI pediátrica, a capacidade de armazenar equipamento e provisões adequados e o desenvolvimento de um centro de comando que possa supervisionar as operações. Estas necessidades só ocorrem após a criação de uma forte liderança organizacional que se possa concentrar nestes aspetos, mesmo em períodos de crise e de surto. De igual forma, é prudente proporcionar transparência no sistema e aos doentes, mediante a comunicação eficaz de que os padrões de cuidado podem ser diferentes durante uma pandemia do que quando não existe um surto crítico, para que qualquer modelo possa vir a ter sucesso.⁴

Existem algumas preocupações e questões fundamentais que ainda subsistem relativamente a todas estas abordagens e que remetem ao velho ditado "apenas porque sabes fazer algo, não significa que o devas fazer". Em primeiro lugar, os resultados clínicos foram piores ou melhores quando os pediatras cuidaram de doentes adultos? Em segundo lugar, o padrão de cuidados para adultos foi comprometido com atrasos no tratamento devido à falta de experiência com doenças que requerem intervenção atempada, ou seja, atrasos na intervenção coronária percutânea no enfarte do miocárdio ou na administração de alteplase em acidentes cerebrovasculares? Isto pode ser difícil de determinar, uma vez que ocorreram atrasos nos cuidados em todos os sistemas de saúde com o fluxo de doentes com COVID-19. No entanto, estas são preocupações importantes que devem ser avaliadas em todos os modelos para ver se um método teve melhores resultados. Em terceiro lugar, o fluxo de trabalho da UCI e o pessoal da UCI precisaram de ser alterados nas UCI pediátricas no caso de os doentes adultos triados terem ou não COVID-

¹Pediatrics, Washington University in St Louis, St Louis, Missouri, USA

²Internal Medicine, Washington University in St Louis, St Louis, Missouri, USA

Correspondence to Dr Kenneth E Remy, Pediatrics, Washington University in St Louis, St Louis, MO 63110, USA; kremy@wustl.edu

Table 1 Modelos de médicos pediatras para o tratamento de adultos gravemente doentes

	Adultos numa UCI pediátrica	Adultos e crianças em UCI pediátrica	Médico de UCI pediátrica a cobrir uma nova UCI de adultos
Pessoal	▶ Médicos, enfermeiros e terapeutas com formação em pediatria ▶ Com experiência a trabalhar juntos em equipa	▶ Médicos, enfermeiros e terapeutas com formação em pediatria ▶ Com experiência a trabalhar juntos em equipa	▶ Com formação dupla em doentes adultos e pediátricos ▶ Sem experiência a trabalhar juntos em equipa
Equipamento	▶ Nova cadeia de aprovisionamento ▶ Novo espaço para provisões	▶ Nova cadeia de aprovisionamento ▶ Novo espaço para provisões ▶ Fardo de manutenção de provisões para doentes adultos e pediátricos	▶ Cadeia de aprovisionamento atual
Cuidados clínicos	▶ Novo processo de transporte e triagem de doentes ▶ Acesso limitado ou inexistente a especialistas de cuidado de adultos ▶ Fardo para especialistas de cuidado pediátrico	▶ Novo processo de transporte e triagem de doentes ▶ Acesso limitado ou inexistente a especialistas de cuidado de adultos ▶ Fardo para especialistas de cuidado pediátrico	▶ Nova unidade mas processo conhecido para transporte e triagem de doentes ▶ Acesso total a especialistas de cuidado de adultos
Comunicação	▶ Estrutura atual, familiaridade e processos conhecidos dos membros da equipa para manter a continuidade dos cuidados	▶ Estrutura atual, familiaridade e processos conhecidos dos membros da equipa para manter a continuidade dos cuidados	▶ Equipa médica recém-criada, com vários antecedentes num novo sistema

UCI, unidade de cuidados intensivos.

19? Ou seja, numa pandemia, é prático triar o doente com a “doença pandémica” para estes cenários ou, em vez disso, triar os doentes com doenças de adultos conhecidas (isto é, agudização da doença pulmonar obstrutiva crónica, pancreatite, cetoacidose diabética, estado hiperosmolar hiperglicémico) para o contexto da UCI pediátrica ou para médicos pediatras? Finalmente, com médicos e enfermeiros pediátricos internos com formação dupla, será que deveria haver uma mudança na formação dos médicos e enfermeiros para uma formação mais direcionada para adultos (ou crianças) para que possam desenvolver uma familiaridade na gestão clínica?

Esta formação pode ser determinante à medida que trabalhamos para futuras pandemias, especialmente porque a sua frequência parece ter aumentado nos últimos 20 anos (SARS, Zika, Ebola, COVID-19). As respostas a estas questões, com uma avaliação rigorosa que não se limite ao “fomos capazes de fazer algo”, mas tente atingir o “fomos capazes de o fazer de uma forma que proporcionou resultados iguais ou mesmo melhores para os doentes”, são

da maior importância para considerações futuras. No entanto, a pandemia da COVID-19 demonstrou, inegavelmente, sob tempos de grande pressão para a profissão médica, o melhor da colegialidade e da verdadeira humanidade. A capacidade de gerir doentes fora do âmbito das práticas padrão para satisfazer as necessidades de um país que surge após um planeamento estratégico cuidadoso e ponderado proporciona esperança a muitas outras regiões que necessitam de orientação para esta ou qualquer outra pandemia no futuro.

As premissas dos surtos críticos e dos planos de implementação não mudaram *per se* nesta pandemia, mas a forma e o alcance da sua aplicação, por necessidade, alteraram a forma como os sistemas podem ter de abordar a prestação de cuidados de saúde a instituições, regiões e países. Novos métodos de simulação de sistemas e UCI podem refinar ainda mais a metodologia, a dinâmica de sistemas, a modelização de grupos e melhorar a rápida implementação para responder mais rapidamente às necessidades mais urgentes em futuras pandemias. Felizmente, estas experiências de sucesso

com a reorganização das UCI são possíveis numa altura em que os doentes pediátricos não são amplamente afetados. Contudo, as lições aprendidas com estes preparativos são extremamente importantes, uma vez que o potencial para uma futura pandemia que afete tanto adultos como as crianças pode apresentar desafios imprevisíveis.

Correction notice This article has been amended since it was published online. The affiliation for the first author has been corrected.

Twitter Kenneth E Remy @drkenremy1

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ORCID iDs

Kenneth E Remy <http://orcid.org/0000-0001-5222-9884>

REFERENCES

- Kim L, Whitaker M, O'Halloran A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1–July 25, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1081–8.
- Medicine SoCC. United States resource availability for COVID-19. Available: <https://www.sccm.org/Blog/March-2020/United-States-Resource-Availability-for-COVID-19>
- Sinha R, Aramburo A, Deep A, et al. Caring for critically ill adults in paediatric intensive care units in England during the COVID-19 pandemic: planning, implementation and lessons for the future. Arch Dis Child 2021;106:548–57.
- Remy KE, Verhoef PA, Malone JR, et al. Caring for critically ill adults with coronavirus disease 2019 in a PICU: recommendations by dual trained intensivists. Pediatr Crit Care Med 2020;21:607–19.
- Christian MD, Kissoon N. Caring for Critically Ill Adults in PICUs Is Not “Child’s Play”. Pediatr Crit Care Med 2020;21:679–81.

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ARTIGO ORIGINAL INVESTIGAÇÃO

Trabalhar no turno da noite está associado a um risco acrescido de asma

Robert J Maidstone,^{1,2} James Turner,³ Celine Vetter,^{4,5} Hassan S Dashti,^{5,6,7} Richa Saxena,^{5,6,7} Frank A J L Scheer,^{8,9,10} Steven A Shea,¹¹ Simon D Kyle,¹² Deborah A Lawlor,^{13,14} Andrew S I Loudon,¹⁵ John F Blaikley,^{16,17} Martin K Rutter,^{15,18} David W Ray,^{2,15,19} Hannah Jane Durrington^{16,17}

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For numbered affiliations see end of article.

Correspondence to

Dr Hannah Jane Durrington, School of Biological Sciences, University of Manchester, Manchester M13 9PL, UK; hannah.durrington@manchester.ac.uk

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RESUMO

Introdução O trabalho por turnos provoca um desalinhamento entre o tempo circadiano interno e o ciclo luz/obscuridade externo e está associado a perturbações metabólicas e cancro. Aproximadamente 20% da população ativa nos países industrializados trabalha em turnos noturnos permanentes ou rotativos, expondo esta grande população ao risco de doença provocada por desalinhamento circadiano. É necessária uma análise do impacto do trabalho por turnos nas doenças inflamatórias crônicas. Investigámos a associação entre o trabalho por turnos e a asma.

Métodos Descrevemos a relação transversal entre o trabalho por turnos e a asma prevalente em >280000 participantes do *UK Biobank*, fazendo ajustamentos para os principais fatores confundidores (histórico de tabagismo, etnia, estatuto socioeconómico, atividade física, índice de massa corporal). Também investigámos o cronotipo.

Resultados Em comparação com os trabalhadores diurnos, os trabalhadores noturnos 'permanentes' apresentaram uma maior probabilidade de asma moderada a grave (OR 1,36 (95% IC 1,03 a 1,8)) e de todos os níveis de asma (OR 1,23 (95% IC 1,03 a 1,46)). Os indivíduos que efetuavam qualquer tipo de trabalho por turnos apresentaram maiores probabilidades ajustadas de sibilância torácica. Os trabalhadores por turnos que nunca ou raramente trabalhavam à noite e as pessoas que trabalhavam permanentemente à noite apresentaram uma maior probabilidade ajustada de redução da função pulmonar (FEV1 <80% previsto). Encontrámos um aumento do risco de asma moderada a grave nos cronotipos matinais que trabalham em turnos irregulares, incluindo noites [OR 1,55 (95% IC 1,06 a 2,27)].

Conclusões As implicações destas conclusões para a saúde pública são de grande alcance devido à elevada prevalência e concorrência, tanto da asma como do trabalho por turnos. São necessários estudos futuros longitudinais de seguimento para determinar se a alteração dos horários de trabalho por turnos, tendo em conta o cronotipo, poderá apresentar-se como uma medida de saúde pública para reduzir o risco de desenvolvimento de doenças inflamatórias como a asma.

INTRODUCTION

Most human biological processes are regulated by an internal circadian timing system to optimally prepare physiological functions for anticipated daily environmental and behavioural cycles. Cyclical light/dark environmental cues, mealtimes and physical activity can serve as 'Zeitgebers' for circadian timing. The development of artificial light has allowed extension of the active period of humans into the night, and through the night for night shift workers. This imbalance between our internal clock and the environment results in circadian misalignment.¹ Shift work, a notable example of circadian misalignment, is invariably associated with sleep disruption and with increased risk of prevalent chronic diseases including metabolic

Key messages**What is the key question?**

► Shift workers are at increased risk of cardiometabolic disorders and cancers. The mechanism is thought to involve circadian misalignment. In this study, using data from >280 000 individuals in the UK Biobank, we asked whether shift workers were at increased risk of asthma.

What is the bottom line?

► Shift workers, especially those working permanent night shifts, had an increased risk of asthma (especially moderate-severe asthma).

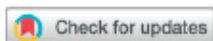
Why read on?

► The public health implications of our findings are potentially far-reaching, since both shift work and asthma are common in the industrialised world. Future longitudinal follow-up studies might determine whether an individual is suited to night shift work based on their chronotype. Currently there are no guidelines for the management of asthma in shift workers. We hope that our study might fuel future discussion in this area.

and cardiovascular diseases^{2,3} and cancer.⁴ There is evidence of causal relationships between circadian misalignment and the development of metabolic and cardiovascular diseases.^{5,6}

Approximately 20% of the working population in industrialised countries work permanent or rotating night shifts,⁷ exposing this large population to the risk of circadian misalignment-driven disease, making this an important area of investigation. Analysis of the impact of shift work on chronic inflammatory diseases is lacking.

Asthma is a very common chronic inflammatory disease of the airways, affecting 339 million people worldwide⁸ and costing the UK public sector £1.1 billion.⁹ Intriguingly, asthma displays marked time of day variations in symptoms (wheeze and whistling),¹⁰ airway calibre¹¹ and in underpinning inflammatory pathways.¹² The physiological diurnal variation in airway calibre is under direct circadian control, independent of external environmental cues such as light/dark and fasting/feeding.¹³ In asthma it appears that the physiological diurnal variation in airway calibre is amplified, suggesting coupling between the internal body clock and pathogenic processes. This raises the possibility that misalignment between the internal body clock and



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the environment, such as that induced by night shift work, would impact on asthma risk. Indeed, a correlation between shift work and work-related asthma was found in a study of 544 individuals working in a cabling manufacturing plant;¹⁴ however, small numbers and confounding limit generalisability. We therefore investigated the association between shift work and asthma in a much larger dataset from the UK Biobank¹⁵ in which we could also adjust for numerous major confounding factors.

We hypothesised that, when compared with day workers, shift work—especially involving nights—would be associated with a higher prevalence of asthma.

The primary outcome was risk of asthma in shift workers. Secondary outcome measures included risk of symptoms of asthma and lung function in shift workers, as well as assessment of the effects of lifetime duration of night shift work and night shift frequency on the risk of asthma.

We also investigated whether chronotype is associated with the risk of asthma in shift workers. Chronotype is the phenotypic expression of the internal circadian timing system and can affect how an individual adapts to shift work; earlier chronotypes experience shortened sleep duration and increased sleep disturbance during night shifts, whereas late chronotypes show similar disruption when working early shifts.¹⁶ Matching shift work patterns to chronotype can improve sleep quality and well-being.¹⁷

Lastly, we investigated the intersection between the genetic risk of asthma and shift work exposure. Asthma risk was captured using a genetic risk score (GRS), the sum of genetic variants with weighted effect sizes.¹⁸ If the asthma GRS affects the health impact of shift work exposure, this may provide an employment screening opportunity in the future.

METHODS

The UK Biobank recruited 502 540 participants (5% of those invited) aged 40–69 years who were registered with the National Health Service (NHS) and lived within reasonable travelling distance of 22 assessment centres across the UK between 2007 and 2010.¹⁹ At the baseline visit, participants completed questionnaires on lifestyle, medical history, occupation and work hours. Trained health professionals asked further details about medical conditions, health status and medications. The selection of participants analysed in all comparisons are shown in a STROBE diagram (online supplemental figure 1) and further information can be found in the online supplemental methods.

Analysis of shift work was restricted to participants in paid employment or who were self-employed at baseline ($n=286\,825$, age range 37–72 years);² we did not exclude any individuals based on other diagnoses. The demographics of this group are shown in table 1. Of these, 83% were day workers and 17% worked shifts, of which 51% included night shifts. Compared with day workers, shift workers were more likely to be male, lived in more deprived neighbourhoods (Townsend area deprivation Index), more likely to live in an urban area and more likely to be smokers. Shift workers drank less alcohol, reported shorter sleep duration and longer weekly working hours. Night shift workers were more likely evening chronotypes compared with those working days. Compared with day workers, shift workers were more likely to have a diagnosis of gastro-oesophageal reflux, chronic obstructive pulmonary disease (COPD)/emphysema, higher cholesterol and hypertension. Shift workers were more likely of non-European ancestry and to be in jobs linked to occupational asthma or to jobs that require a medical examination. There were differences between the proportion of workers in each employment category across the work schedules. Night shift workers were more likely to work in the service occupations or as process, plant and machine operatives. In contrast, day workers tended to be in administrative roles and in professional occupations (online supplemental table 1).

Cases of asthma

Cases of asthma were defined by including all participants with self-reported doctor-diagnosed asthma at baseline who were also receiving any asthma medication.²⁰ Using these criteria, we identified 14 238 (5.3%) cases, of which 4783 (1.9%) had moderate-se-

vere asthma (defined as having doctor-diagnosed asthma at baseline and currently taking medication in accordance with steps 3–5 of the British Thoracic Society guidance for the treatment of asthma).²⁰ We excluded from our analyses participants with doctor-diagnosed asthma who did not report taking asthma medication as well as those participants reporting taking asthma medication who did not have doctor-diagnosed asthma ($n=20\,151$). For analysis of moderate-severe asthma, we further excluded those not on medication for moderate-severe asthma (listed in the Methods section, $n=9455$). Initially, we focused on those with moderate-severe asthma, since these individuals were more likely to have active asthma requiring regular disease modifying treatment, so reducing the risk of misdiagnosis.

Statistical analysis

We fitted a multivariate logistic regression model to the data and used this to estimate adjusted ORs and 95% asymptotic CIs on those ORs.

In model 1 we initially adjust for participant age and sex. We extend this in model 2 to additionally include BMI, ethnicity, chronotype, Townsend Deprivation Index (TDI), days exercised, smoker status (current, previous or never) and pack-years smoked, alcohol status (current, previous or never) and alcohol weekly intake, length of working week and whether current job is considered to have an occupational asthma risk or requires a medical examination prior to hiring. These covariates were chosen by consideration of participant characteristics (table 1). Model 3 also included sleep duration in addition to covariates in model 2.

RESULTS

In an age- and sex-adjusted model, there were higher odds of having moderate-severe asthma in shift workers who never or rarely undertook night shifts (OR 1.12 (95% CI 1.02 to 1.24) and in those on permanent night shifts (OR 1.21 (95% CI 1.02 to 1.44)) when compared with day workers (figure 1). After further adjusting for smoking status and pack years, alcohol status and intake, ethnicity, social deprivation, physical activity, BMI, chronotype, length of working week, job asthma risk and job medical examination required (Model 2), associations attenuated in shift workers who never or rarely undertook night shifts (OR 1.17 (95% CI 0.98 to 1.38)) and slightly increased in permanent night shift workers (OR 1.36 (95% CI 1.03 to 1.8)). Further adjustment for sleep duration had no additional effects on the estimates (Model 3).

A similar pattern of higher odds of asthma was seen when all cases of asthma were considered (see online supplemental table 2). In an age- and sex-adjusted model, we observed higher odds of asthma in shift workers who never or rarely worked night shifts when compared with day workers (OR 1.08 (95% CI 1.02 to 1.15)). However, this association attenuated to the null with covariate adjustment (Model 2). The odds of asthma in shift workers working permanent nights were higher in covariate-adjusted models (Model 2: OR 1.23 (95% CI 1.03 to 1.46); Model 3: OR 1.20 (95% CI 1.01 to 1.43)) than in the age- and sex-adjusted model.

Symptoms of asthma

We then analysed the association between shift work and the experience of wheeze or whistling in the chest in the previous year ($n=280\,998$). When compared with day workers, the age and sex-adjusted model revealed higher odds for these symptoms in association with all three types of shift work (shift work but never or rarely night shifts, irregular night shifts and permanent nights; figure 2). These associations with wheeze or whistling were attenuated but remained statistically significant for all types of shift work in Models 2 and 3 (eg, Model 2: shift work, but never or rarely night shifts: OR 1.11 (95% CI 1.05 to 1.18); irregular shift work including nights: 1.21 (95% CI 1.14 to 1.29); and permanent night shift work: 1.18 (95% CI 1.08 to 1.30)).

Reduced lung function

We also examined the association between shift work status and reduced lung function assessed as the proportion of participants with a forced expiratory volume in 1 s (FEV_1) that was <80% of the predicted value based on height and age ($n=89\,157$). In age- and sex-adjusted models there were higher odds of participants having an FEV_1 <80% predicted in all shift work groups compared with day workers (table 2). After multivariable adjustment, these associations attenuated

Table 1 Clinical characteristics by current shift work exposure (n=286 825)

	Current work schedule			
	Day workers	Shift work, but never or rarely night shifts	Irregular shift work including nights	Permanent night shift work
N	236 897	24 560	18 226	7142
Age, years	52.90 (7.13)	52.48 (7.08)	51.08 (6.87)	51.45 (6.91)
Sex (% male)	46.58	47.51	62.43	61.43
BMI, kg/m ²	27.09 (4.65)	27.79 (4.99)	28.21 (4.91)	28.51 (4.88)
Smoker, %				
Never	58.10	53.66	52.82	51.99
Previous	31.91	32.11	30.52	30.03
Current	9.75	13.88	16.19	17.67
Smoking, pack-years	20.07 (16.07)	22.92 (17.49)	24.31 (17.77)	25.70 (18.38)
Daily alcohol intake, %	20.48	16.89	15.98	10.21
Sleep duration (hours)	7.05 (1.03)	6.95 (1.22)	6.85 (1.30)	6.67 (1.52)
Morning chronotype, %	23.33	25.49	22.85	19.24
Evening chronotype, %	8.02	7.87	9.83	16.90
Ethnicity (%)				
White British	88.47	83.30	79.87	80.99
White other	6.45	7.07	7.03	6.01
Mixed	0.65	0.90	0.97	0.87
Asian	1.72	3.58	3.84	3.39
Black	1.40	2.69	4.93	5.47
Chinese	0.34	0.48	0.46	0.67
Other	0.09	0.13	0.10	0.14
Weekly work hours	34.24 (13.19)	34.97 (13.21)	39.29 (14.55)	39.59 (13.73)
Job asthma risk (%)	7.59	7.18	8.11	7.74
Job medical required (%)	2.27	2.52	4.14	3.68
Single occupancy (%)	15.64	18.78	18.71	18.42
Urban area (%)	85.98	89.59	89.33	90.97
Townsend Index	-2.24 (-3.70 to 0.19)	-1.31 (-3.18 to 1.61)	-1.24 (-3.17 to 1.82)	-1.04 (-3.02 to 2.07)
Maternal smoking (%)	26.59	28.88	29.23	30.75
Breastfed as baby (%)	56.12	54.27	54.16	51.51
Birth weight (kg)	3.33 (0.63)	3.31 (0.68)	3.35 (0.67)	3.31 (0.71)
Hypertension (%)	19.75	21.58	21.64	22.81
High cholesterol (%)	7.88	8.55	8.54	9.27
Sleep apnoea (%)	0.28	0.30	0.42	0.27
COPD/ emphysema/chronic bronchitis (%)	0.81	1.26	1.27	1.23
Bronchiectasis (%)	0.14	0.12	0.03	0.14
Interstitial lung disease (%)	0.02	0.01	0.03	0.01
Other respiratory problems (%)	0.12	0.17	0.16	0.07
Gastro-oesophageal reflux (%)	3.19	3.65	3.84	4.16

Data are mean (SD), median (IQR) or percentages. Positive values of the Townsend Index indicate high material deprivation, negative values indicate relative affluence. The diagnosis of conditions (hypertension, high cholesterol, sleep apnoea, COPD/emphysema/chronic bronchitis, bronchiectasis, interstitial lung disease, other respiratory problems and gastro-oesophageal reflux) came from participants self-reporting a doctor diagnosis.

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

ted towards the null with higher odds remaining for shift workers who never or rarely worked night shifts and for those working permanent nights (eg, Model 2: shift work, but never or rarely night shifts: OR 1.19 (95% CI 1.08 to 1.32); permanent night shift work: OR 1.20 (95% CI 1.03 to 1.41) compared with day workers).

Lifetime duration of night shift work

Next we used data on 107 930 participants who provided lifetime work history data. When compared with those reporting no history of shift work, the highest odds for moderate-severe asthma was seen in participants reporting <5 years of shift work (OR 1.34 (95% CI 1.08 to 1.66)) and the lowest odds when performing ≥10 years of shift work (OR 1.22 (95% CI 1.08 to 1.38)) (figure 3A). In participants reporting <5 years of shift work, high point estimates for odds for moderate-severe asthma remained after adjusting for covariates in Models 2 and 3, but relationships were attenuated to the null for those with higher lifetime durations. No strong statistical evidence of a trend was found when treating lifetime duration of shift work as a continuous variable in any model.

Average lifetime night shift frequency

Using the same historical lifetime work data, we analysed the prior frequency of night shift work in relation to the prevalence of moderate-severe asthma (n=107 930; figure 3B). In age- and sex-adjusted

models, when compared with participants reporting no shift work, there were higher odds of moderate-severe asthma in people reporting prior higher frequencies of night shift work (5–10 night shifts/month): OR 1.22 (95% CI 1.05 to 1.42) and also ≥10 night shifts/month: OR 1.31 (95% CI 1.12 to 1.54), but not the lower frequency of shift work (<5 night shifts/month): OR 1.16 (95% CI 0.97 to 1.38). However, these associations attenuated to the null on covariate adjustment (Models 2 and 3). There was no strong statistical evidence of average lifetime frequency of night shift work as a continuous variable associating with asthma in any model.

Chronotype

We analysed the likelihood of asthma by chronotype in all UK Biobank participants (n=413 040; table 3). People reporting either extreme chronotype (definitely a morning person or definitely an evening person) had higher odds of having any asthma compared with those describing themselves as intermediate chronotypes. After adjustment for covariates, the ORs for asthma in those reporting being definitely a morning person were 1.12 (95% CI 1.03 to 1.21) and 1.16 (95% CI 1.04 to 1.28) for those reporting being definitely an evening person (Model 3).

When we assessed the likelihood of moderate-severe asthma in relation to chronotype (n=398 252), age- and sex-adjusted models showed higher odds for moderate-severe asthma for people with either extreme chronotype compared with people with intermediate chro-

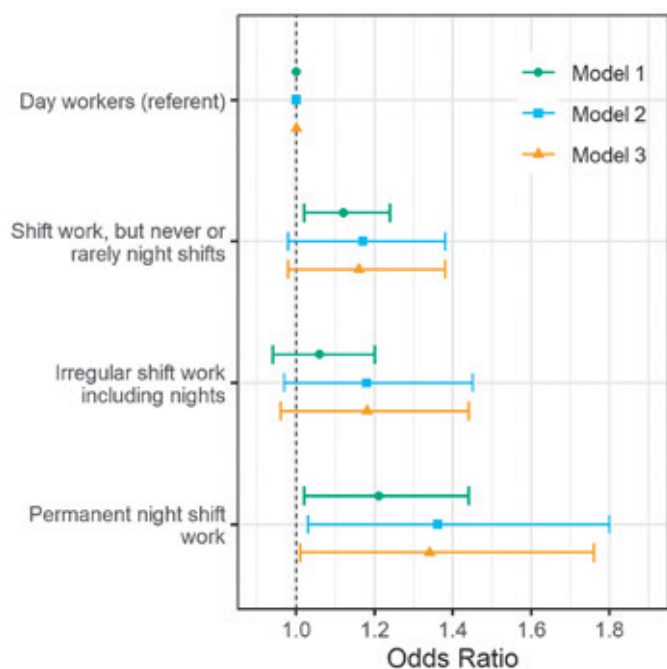


Figure 1 Adjusted odds of moderate-severe asthma by current shift work exposure (n=257 219). Forest plot of adjusted ORs with corresponding 95% asymptotic CIs for moderate-severe asthma stratified by current work pattern. Three multivariate logistic regression models were fitted to the data: Model 1 (green circle): age- and sex-adjusted. Model 2 (blue square) covariates: age, sex, smoking status, smoking pack-years, alcohol status, daily alcohol intake, ethnicity, Townsend Deprivation Index, days exercised (walked, moderate and vigorous), body mass index, chronotype, length of working week, job asthma risk and job medical required. Model 3 (yellow triangle): model 2 covariates plus sleep duration.

notypes (see online supplemental table 3). Results for definitely an evening person attenuated to the null after covariate adjustment (eg, Model 3: OR 1.17 (95% CI 0.99 to 1.38)); attenuation was less for definitely a morning person (eg, Model 3: OR 1.19 (95% CI 1.05 to 1.35)).

Finally, in relation to chronotype, we assessed the likelihood of moderate-severe asthma in individuals with a definite morning chronotype by shift work pattern (n=59 621; online supplemental table 4). In participants who reported being definitely a morning person there was a higher odds of moderate-severe asthma in covariate-adjusted models in those working irregular shifts, including nights, compared with those working day shifts (eg, Model 2: OR 1.55 (95% CI 1.06 to 2.27)). There was no excess risk for those morning chronotype workers either on permanent night shifts or rarely working nights.

There was no strong evidence of associations between shift work pattern and the likelihood of moderate-severe asthma when we restricted our analysis to individuals who reported being definitely an evening person (n=20 834) or being an intermediate chronotype (n=148 216) (see online supplemental table 4). There was no statistical evidence of an interaction between chronotype and shift work in association with asthma ($p_{\text{interaction}}=0.21$).

Asthma Genetic Risk Score (GRS)

We examined whether genetic susceptibility for asthma modified the relationship between shift work and the likelihood of asthma. In those of European ancestry in the UK Biobank cohort, we first

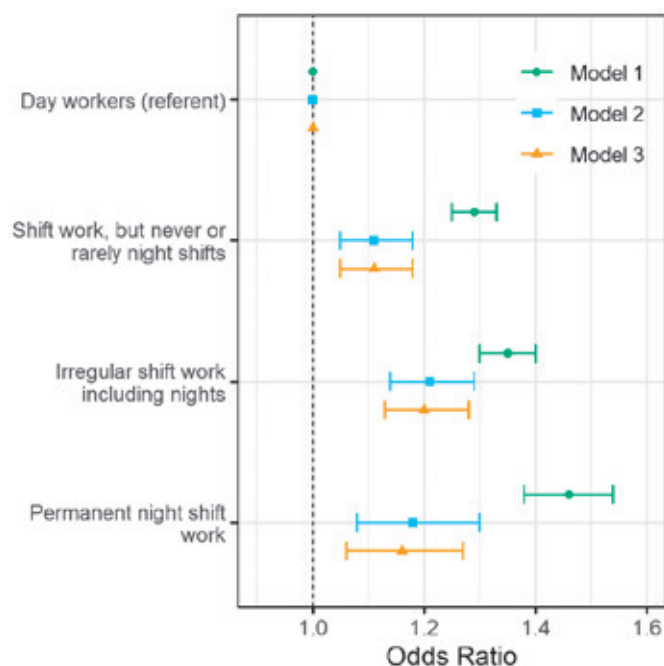


Figure 2 Adjusted odds of experiencing wheeze or whistling in the chest in the last year by current shift work exposure (n=280 998). Forest plot of adjusted ORs with corresponding 95% asymptotic CIs for experiencing wheeze or whistling in the chest in the last year stratified by current work pattern. Three multivariate logistic regression models were fitted to the data: Model 1 (green circle): age- and sex-adjusted. Model 2 (blue square) covariates: age, sex, smoking status, smoking pack-years, alcohol status, daily alcohol intake, ethnicity, Townsend Deprivation Index, days exercised (walked, moderate and vigorous), body mass index, chronotype, length of working week, job asthma risk and job medical required. Model 3 (yellow triangle): Model 2 covariates plus sleep duration.

showed that a higher genetic risk for asthma was associated with a higher odds of moderate-severe asthma (Model 2: per risk allele OR 1.13 (95% CI 1.11 to 1.16), $p_{\text{trend}} < 0.01$, n=313 816) and for risk of any asthma (Model 2: per risk allele OR 1.12 (95% CI 1.10 to 1.13), $p_{\text{trend}} < 0.01$, n=302 686). To investigate this effect further we split the GRS into quartiles and calculated odds of any asthma (online supplemental table 5) and moderate-severe asthma (online supplemental table 6) on these quartiles. Using the quartiles of GRS for moderate-severe asthma, we found that the asthma GRS had a statistically significant interaction on the relationships between odds for moderate-severe asthma and current shift work schedule ($p < 0.05$). However, this interaction did not appear linear in its effects. Odds were higher for moderate-severe asthma in shift workers (who never or rarely worked night shifts) in the second GRS quartile (OR 1.78 (95% CI 1.17 to 2.68)) and also in permanent night shift workers in the third GRS quartile (OR 2.04 (95% CI 1.11 to 3.74), online supplemental table 7).

Chronic obstructive pulmonary disease (COPD), emphysema and chronic bronchitis

Our definition of asthma may have included participants who had a concurrent doctor diagnosis of COPD, emphysema or chronic bronchitis since some medications are used to treat all conditions. There is no way of determining which condition is predominant among UK

Table 2 Adjusted odds (95% CI) of having a critical FEV₁ predicted percentage (<80%) by current shift work exposure (n=89 157)

	Current work schedule			
	Day workers	Shift work, but never or rarely night shifts	Irregular shift work including nights	Permanent night shift work
Total cases (% of total sample size)	9381 (12.73%)	1183 (15.84%)	849 (15.07%)	397 (16.99%)
Total sample size	73 719	7469	5632	2337
Model 1: Age- and sex-adjusted OR (95% CI)	1 (referent)	1.31 (1.23 to 1.40)	1.27 (1.18 to 1.37)	1.44 (1.29 to 1.61)
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.19 (1.08 to 1.32)	1.08 (0.96 to 1.21)	1.20 (1.03 to 1.41)
Model 3: Model 2 covariates+sleep duration OR (95% CI)	1 (referent)	1.19 (1.08 to 1.32)	1.08 (0.97 to 1.21)	1.21 (1.04 to 1.42)

The predicted FEV₁ was estimated based on height and age. Model 2 covariates: age, sex, smoking status, smoking pack-years, alcohol status, daily alcohol intake, ethnicity, Townsend Deprivation Index, days exercised (walked, moderate and vigorous), body mass index, chronotype, length of working week, job asthma risk and job medical required.

Model 3 data are adjusted for Model 2 covariates plus sleep duration. FEV₁, forced expiratory volume in 1 s.

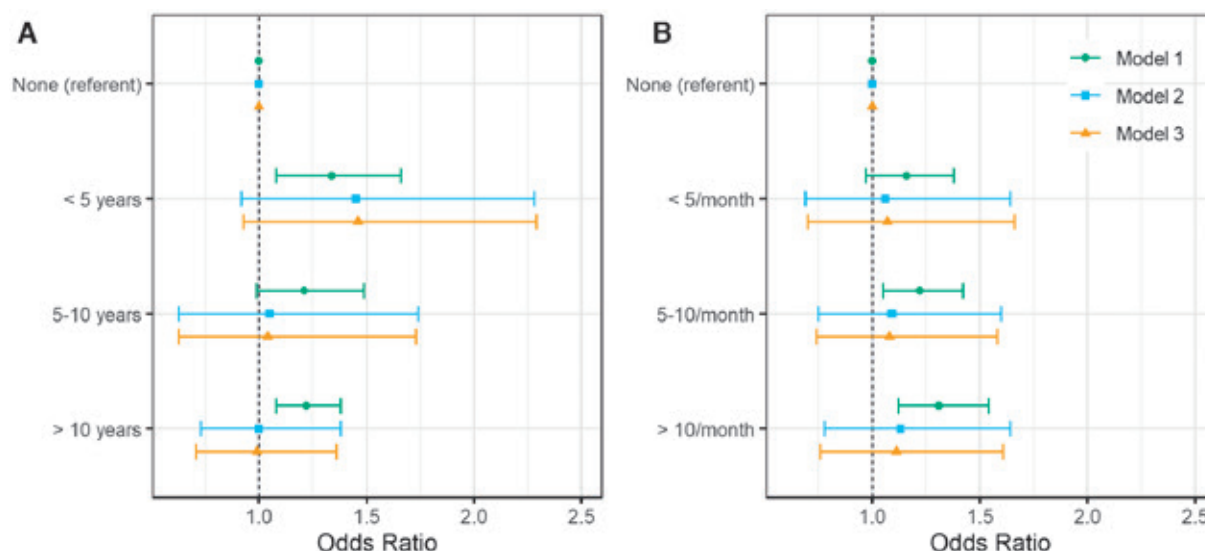


Figure 3 Adjusted odds of experiencing wheeze or whistling in the chest in the last year by current shift work exposure (n=280 998). Forest plot of adjusted ORs with corresponding 95% asymptotic CIs for experiencing wheeze or whistling in the chest in the last year stratified by current work pattern. Three multivariate logistic regression models were fitted to the data: Model 1 (green circle): age- and sex-adjusted. Model 2 (blue square) covariates: age, sex, smoking status, smoking pack-years, alcohol status, daily alcohol intake, ethnicity, Townsend Deprivation Index, days exercised (walked, moderate and vigorous), body mass index, chronotype, length of working week, job asthma risk and job medical required. Model 3 (yellow triangle): Model 2 covariates plus sleep duration.

Biobank participants, therefore we re-analysed the cohort after excluding all cases of concurrent doctor-diagnosed COPD, emphysema and chronic bronchitis. A total of 1790 participants were removed from the any asthma group and 1572 participants from the moderate-severe asthma group. Our results were similar to our previous findings: for moderate-severe asthma we found, in an age- and sex-adjusted model, there was a higher odds of having moderate-severe asthma in day shift workers who never or rarely undertook night shifts (OR 1.12 (95% CI 1.01 to 1.24)) when compared with day workers (see online supplemental table 8). After adjusting for additional covariates (Model 2), only permanent night shift workers had a significantly higher likelihood of asthma (OR 1.35 (95% CI 1.01 to 1.82)). Further adjustment for sleep duration slightly attenuated the likelihood of moderate-severe asthma in permanent night shift workers (OR 1.33 (95% CI 0.99 to 1.79)). In an age- and sex-adjusted model, we observed a higher likelihood of asthma in shift workers who never or rarely worked night shifts when compared with day workers (OR 1.07 (95% CI 1.01 to 1.14)). However, this association attenuated to the null after adjusting for additional covariates (Model 2). In contrast, the likelihood of asthma in shift workers working permanent nights was statistically significant in multivariable adjusted models (Model 2: OR 1.26 (95% CI 1.05 to 1.50); Model 3: OR 1.23 (95% CI 1.03 to 1.48); see online supplemental table 9).

DISCUSSION

This study shows that, compared with day workers: (a) people working permanent nights had higher adjusted odds of moderate-severe asthma; (b) people doing any type of shift work had higher adjusted odds of wheeze or whistling in the chest; (c) shift workers who never or rarely worked on nights and people working permanent nights had a higher adjusted likelihood of having reduced lung function ($FEV_1 < 80\%$ predicted). We analysed data from more than 280 000 UK Biobank participants, 17% of whom were shift workers, which is similar to the reported prevalence of shift work in other industrialised countries.⁷

Rotational shift work disrupts the entrainment of endogenous circadian rhythms to external cues in the environment, resulting in circadian misalignment.²¹ Shift workers, especially those working night shifts, sleep at an inappropriate circadian phase, causing circadian misalignment between their sleep/wake behaviour and endogenous circadian processes. Mouse models of shift work have shown that it is the phase misalignment between the internal clockwork and behaviour that drives many of the resulting pathologies.²² To date, the association between asthma and circadian misalignment has not been investigated. We discover that night shift work associates with an increased risk of asthma.

As the UK Biobank data are drawn from a cross-sectional observational study, no causal inference is possible. However, it is plausible that circadian misalignment leads to asthma development. To investigate this we looked at people with extreme chronotypes (morning/evening preferences) who experience a degree of circadian misalignment in the absence of shift work exposure. We found that extreme chronotypes were significantly more likely to have asthma even after multivariable adjustments. The majority of individuals in our analysis were day workers (n=236 897), therefore the higher likelihood of asthma in evening types may represent circadian misalignment caused through conforming to early day shift working hours.²³ In support of our findings, previous smaller studies have shown that evening or intermediate chronotypes associate with asthma.²⁴ Our analysis of chronotype included data from 413 040 individuals including 9604 people with moderate-severe asthma. When we analysed chronotype in the context of type of shift work, we found that there was an increase in moderate/severe asthma risk in morning chronotypes working irregular shifts, including nights (OR 1.55 (95% CI 1.06 to 2.27)). Morning types find it particularly difficult to adjust to working night shifts²⁵ and display the highest levels of circadian misalignment. Evening chronotypes showed no increase in the risk of asthma after shift work exposure, raising the intriguing possibility that evening chronotypes might be protected from the effects of shift work on asthma risk. Interestingly, chronotype does change with age, getting later through adolescence

Table 3 Adjusted odds (95% CI) of any asthma by chronotype (n=413 040)

	Chronotype		
	Intermediate chronotype	Definitely a morning person	Definitely an evening person
Total cases (% of total sample size)	15 010 (5.68%)	6786 (6.06%)	2596 (7.06%)
Total sample size	264 279	112 007	36 754
Model 1: Age- and sex-adjusted OR (95% CI)	1 (referent)	1.07 (1.04 to 1.10)	1.27 (1.22 to 1.33)
Model 2: Multivariable adjusted OR (95% CI)	1 (referent)	1.12 (1.04 to 1.22)	1.16 (1.05 to 1.29)
Model 3: Model 2 covariates+sleep duration OR (95% CI)	1 (referent)	1.12 (1.03 to 1.21)	1.16 (1.04 to 1.28)

Model 2 covariates: age, sex, smoking status, smoking pack-years, alcohol status, daily alcohol intake, ethnicity, Townsend Deprivation Index, days exercised (walked, moderate and vigorous), body mass index, length of working week, job asthma risk and job medical required. Model 3 data are adjusted for Model 2 covariates plus sleep duration.

and then earlier as adults age,²⁶ suggesting that older individuals might find it more difficult to adjust to night shift work than younger adults.

We found that the likelihood for any asthma and moderate-severe asthma was higher in individuals working permanent night shifts than in those working irregular shift work patterns, including nights. One might assume irregular night shifts lead to more circadian misalignment than permanent night shifts; however, only a small minority (<3%) of permanent night shift workers appear to adequately adjust their endogenous circadian timing to night work, as assessed by circadian rhythmicity of melatonin.²⁷

We found a cumulative increase in the odds for moderate-severe asthma in shift workers working more frequent nights; however, this association was attenuated to the null after covariate adjustments and there was no strong statistical evidence when shift work frequency was treated as a continuous variable. We found higher odds of moderate-severe asthma in individuals who had worked night shifts for <5 years and in those who had worked for ≥10 years compared with day workers. The point estimates for the ORs suggested that this association might be stronger in individuals working night shifts for <5 years compared with those who had worked for ≥10 years. We postulate that this might represent the healthy worker effect, where individuals stop working night shifts once their health declines.²⁸ However, these analyses need to be repeated in larger studies.

We devised a GRS for asthma derived from genome-wide association study (GWAS) signals²⁰ and sought evidence that genetic susceptibility for asthma may modify the risk of shift work exposure. However, the emerging data were inconclusive, with associations being apparent in the middle two quarters of the GRS distribution and not consistent with stronger associations at higher genetic liability as we might have expected. Such an intersection between genetic risk of asthma and response to shift work exposure would require replication in a larger cohort.

Our study has several strengths; it involves a large cohort of >280 000 individuals from across the UK, with detailed medical history, current employment information, lifestyle information and demographic details, all of which were collected in a uniform manner. Of these >160 000 also had genetic data available. In addition, >100 000 individuals from the original cohort also provided a detailed employment history.

The study also has some limitations. First, UK Biobank participation rates were low at ~5%, which may have introduced selection bias towards more healthy individuals.²⁹ In fact, the overall prevalence of asthma in all participants studied here was ~5% (also ~5% in the shift worker cohort alone) compared with ~10% within the general population of the UK.³⁰ The UK Biobank provides no data on younger people and only limited data on ethnic minorities. The sample sizes were small for the morning and evening chronotype analyses, which resulted in low power. There was a reduction in sleep duration reported by night shift workers; this would be a potential confounder and so we took self-reported sleep duration into account in Model 3. In fact, we found that Model 3 did not significantly alter the results from Model 2. Furthermore, we determined differences in job type between day workers and shift workers and it is possible that these differences could account for some of our findings. To mitigate this risk, we took into account participants in jobs that might lead to occupational asthma or that required a medical assessment (selecting against asthma).

CONCLUSION

This study shows that there is an increased likelihood of asthma (especially moderate-severe asthma) in shift workers on permanent nights. There are no specific national clinical guidelines for how to manage asthma in shift workers (or, indeed, when to measure lung function in night shift workers); however, modifying shift work schedules to take into account chronotype might present a public health measure to reduce the risk of developing inflammatory diseases such as asthma.

Author affiliations

¹Division of Informatics, Imaging & Data Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

²Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK

³Medical School, University of Manchester, Manchester, UK

⁴Circadian and Sleep Epidemiology Laboratory, Department of Integrative Physiology, University of Colorado at Boulder, Boulder, Colorado, USA

⁵Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA

⁶Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

⁷Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

⁸Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

⁹Medical Chronobiology Program, Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, Massachusetts, USA

¹⁰Division of Sleep Medicine, Harvard Medical School, Boston, Massachusetts, USA

¹¹Oregon Institute of Occupational Health Sciences, Oregon Health & Science University, Portland, Oregon, USA

¹²Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

¹³MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK

¹⁴Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

¹⁵Division of Diabetes, Endocrinology & Gastroenterology, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

¹⁶Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

¹⁷Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester, UK

¹⁸Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

¹⁹NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford, UK, University of Oxford, Oxford, UK

Correction notice This article has been corrected since it was published Online First. Some author names were misspelt and missing middle initials.

Twitter Robert J Maidstone @robertmaidstone and Hannah Jane Durrington @h_durrington

Contributors HJD, RM, DR and MR conceived the study and planned and conducted it. RM, HJD, JT, MR and DR acquired the data. RM, HJD, JT, MR, DR, HD and RS performed the data analysis. HJD, RM, DR, ASL, JB, RS, CV, FS, SS, SK, DL, HD and MR interpreted the data and wrote the manuscript.

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ORCID iD

Hannah Jane Durrington <http://orcid.org/0000-0002-9990-9446>

REFERENCES

- Smolensky MH, Hermida RC, Reinberg A, et al. Circadian disruption: new clinical perspective of disease pathology and basis for chronotherapeutic intervention. *Chronobiol Int* 2016;33:1101–19.
- Vetter C, Dashi HS, Lane JM, et al. Night shift work, genetic risk, and type 2 diabetes in the UK Biobank. *Diabetes Care* 2018;41:762–9.
- Jankowiak S, Backé E, Liebers F, et al. Current and cumulative night shift work and subclinical atherosclerosis: results of the Gutenberg Health Study. *Int Arch Occup Environ Health* 2016;89:1169–82.
- Węgrzyn LR, Tamiński RM, Rosner BA, et al. Rotating night-shift work and the risk of breast cancer in the Nurses' Health Studies. *Am J Epidemiol* 2017;186:532–40.
- Mason JC, Qian J, Adler GK, et al. Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes. *Diabetologia* 2020;63:462–72.
- Chellappa SL, Vujovic N, Williams JS, et al. Impact of circadian disruption on cardiovascular function and disease. *Trends Endocrinol Metab* 2019;30:767–79.
- Haus E, Smolensky M. Biological clocks and shift work: circadian dysregulation and potential long-term effects. *Cancer Causes Control* 2006;17:489–500.
- The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network 2018.
- Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;14:113.
- Turner-Warwick M. Nocturnal asthma: a study in general practice. *J R Coll Gen Pract* 1989;39:239–43.
- Sutherland ER. Nocturnal asthma. *J Allergy Clin Immunol* 2005;116:1179–86.
- Durrington HJ, Gioan-Tavernier GO, Maidstone RJ, et al. Time of day affects eosinophil biomarkers in asthma: implications for diagnosis and treatment. *Am J Respir Crit Care Med* 2018;198:1578–81.
- Spengler CM, Shea SA. Endogenous circadian rhythm of pulmonary function in healthy humans. *Am J Respir Crit Care Med* 2000;162:1038–46.
- Attarchi M, Dehghan F, Yazdanparast T, et al. Occupational asthma in a cable manufacturing company. *Iran Red Crescent Med J* 2014;16:e9105.
- Palmer LJ. UK Biobank: bank on it. *Lancet* 2007;369:1980–2.
- Juda M, Vetter C, Roenneberg T. Chronotype modulates sleep duration, sleep quality, and social jet lag in shift-workers. *J Biol Rhythms* 2013;28:141–51.
- Vetter C, Fischer D, Matura JL, et al. Aligning shift times with chronotype improves sleep and reduces circadian disruption. *Curr Biol* 2015;25:907–11.
- Vicente CT, Revez JA, Ferreira MAR. Lessons from ten years of genome-wide association studies of asthma. *Clin Transl Immunology* 2017;6:e165.
- Allen NE, Sudlow C, Peakman T, et al. UK Biobank data: come and get it. *Sci Transl Med* 2014;6:224ed4.
- Shrine N, Portelli MA, John C, et al. Moderate-To-Severe asthma in individuals of European ancestry: a genome-wide association study. *Lancet Respir Med* 2019;7:20–34.
- Slatten TL, Cappuccio FP, Davidson AJ, et al. Health consequences of circadian disruption. *Sleep* 2020;43:pii: zsz194.
- West AC, Smith L, Ray DW, et al. Misalignment with the external light environment drives metabolic and cardiac dysfunction. *Nat Commun* 2017;8:417.
- Abbott SM, Reid KJ, Zee PB. Circadian disorders of the sleep-wake cycle. In: Kryger M, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*. 6th edition. Philadelphia: Elsevier, 2016: 414–23.
- Haldar P, Debnath S, Maity SG, et al. Association between asthma and allergic diseases and circadian preference (chronotype) of the adolescents. *ERJ* 2019;54:PA2783.
- Gamble KL, Motsinger-Reif AA, Hida A, et al. Shift work in nurses: contribution of phenotypes and genotypes to adaptation. *PLoS One* 2011;6:e18395.
- Urbanek JK, Spira AP, Di J, et al. Epidemiology of objectively measured bedtime and chronotype in US adolescents and adults: NHANES 2003–2006. *Chronobiol Int* 2018;35:416–34.
- Folkard S. Do permanent night workers show circadian adjustment? A review based on the endogenous melatonin rhythm. *Chronobiol Int* 2008;25:215–24.
- Knutsson A, Åkerstedt T. The healthy-worker effect: self-selection among Swedish shift workers. *Work Stress* 1992;6:163–7.
- Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017;186:1026–34.
- Asthma UK. Stop asthma attacks. cure asthma. Available: www.asthma.org.uk



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

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

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ARTIGO ORIGINAL INVESTIGAÇÃO

Bloqueador do sistema renina-angiotensina e resultados da COVID-19: uma revisão sistemática e meta-análise

Hyun Woo Lee,¹ Chang-Hwan Yoon,² Eun Jin Jang,³ Chang-Hoon Lee⁴

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¹Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, The Republic of Korea

²Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, The Republic of Korea

³Department of Information Statistics, Andong National University, Andong, Gyeongsangbuk-do, The Republic of Korea

⁴Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Jongno-gu, Seoul, The Republic of Korea

Correspondence to

Dr Chang-Hoon Lee, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Jongno-gu 03080, Korea (the Republic of); kauri670@empal.com

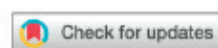
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RESUMO

Contexto A associação de IECA (inibidores da enzima conversora da angiotensina) e bloqueadores de receptores de angiotensina II (BRA) com a gravidade da doença em doentes com COVID-19 ainda não é clara. Realizámos uma revisão sistemática e uma meta-análise para investigar se a utilização de IECA/BRA está associada ao risco de mortalidade e doença grave em doentes com COVID-19.

Métodos Pesquisámos todos os estudos clínicos disponíveis que incluísem doentes com COVID-19 confirmado que pudessem ser classificados num grupo IECA/BRA e num grupo não IECA/BRA até 4 de maio de 2020. Foi realizada uma meta-análise e os resultados primários foram mortalidade por todas as causas e doença grave.

Resultados A utilização de IECA/BRA não aumentou o risco de mortalidade por todas as causas, tanto na meta-análise para 11 estudos com 12 601 doentes que referiram OR (OR=0,52 (95% CI=0,37 a 0,72), certeza moderada da evidência) como em 2 estudos com 8577 doentes que apresentaram HR (*hazard ratio*). Para 12 848 doentes em 13 estudos, a utilização de IECA/BRA não esteve relacionada com um aumento do risco de doença grave na COVID-19 (OR=0,68 (95% IC=0,44 a 1,07); I²=95%, baixa certeza de evidência).

Conclusões A terapêutica IECA/BRA não esteve associada ao aumento do risco de mortalidade por todas as causas ou manifestações graves em doentes com COVID-19. A terapêutica IECA/BRA pode ser continuada sem preocupação de agravamento relacionado com medicamentos em doentes com COVID-19.

INTRODUCTION

As of 9 May 2020, SARS-CoV-2 has infected >3.7 million people and killed >259 000 patients worldwide.¹ However, knowledge of this new virus remains sparse, which is a major hindrance to overcoming the current pandemic. One of the main issues to resolve is whether the use of the renin-angiotensin system blockers, including ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), may be associated with the severity of COVID-19 caused by SARS-CoV-2.

Preclinical studies demonstrated an increase in the expression level of ACE2 in the heart² and kidney³ of rats treated with ARBs, as well as in human intestine biopsies treated with ACEIs.⁴ ACE2 was identified as a functional receptor through which SARS-CoV-2 enters host cells.^{5,6} Therefore, it is reasonable to be concerned that treatment with ACEI/ARB could facilitate virus entry due to increased ACE2 expression, leading to more severe disease. If this is the case, ACEI/ARB should be discontinued in patients who are being treated with these drugs on the confirmation of COVID-19 diagnosis.⁷

This issue is important, given that the duration of the SARS-CoV-2 pandemic remains

Key messages

What is the key question?

► Is there a statistical significance in clinical outcomes, including all-cause mortality and severe disease between ACE inhibitors/angiotensin II receptor blocker (ACEI/ARB) group and non-ACEI/ARB group in patients with COVID-19?

What is the bottom line?

► For 21 178 patients in 13 studies, ACEI/ARB use did not increase the risk of all-cause mortality of patients with COVID-19.
► For 12 848 patients in 13 studies, ACEI/ARB use was not related to an increased risk of severe disease in those with COVID-19.

Why read on?

► Our study supports the current recommendations favouring the continuation of ACEI/ARB use during the COVID-19 pandemic.

unclear,⁸ and ACEI/ARBs are among the most commonly prescribed drugs.^{9,10} Although several professional societies have recommended the continuation of ACEI/ARBs in the current situation,¹¹ uncertainty remains owing to a lack of supporting clinical data.

Although several observational studies have been published recently,^{12–21} they reported somewhat different results. For example, Zhang *et al* showed that ACEI/ARB treatment was associated with a reduced risk of mortality in patients with COVID-19,²¹ but Mancina *et al* showed a higher proportion of ACEI/ARB use among critical patients than among those with mild-to-moderate infection.¹⁴

To help resolve this issue, we conducted a systematic review and meta-analysis on recently published studies to investigate the effects of ACEI/ARBs on the risk of mortality and severe disease in patients diagnosed with COVID-19.

METHODS

Protocol and registration

This systematic review was reported according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology²² and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.²³ The protocol of the systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020179780) on 17 April 2020.

Eligibility criteria

The eligibility criteria for studies included in the systematic review were as follows: (1) the study subjects were diagnosed with COVID-19 by high-throughput sequencing or real-time reverse transcription-PCR assay using upper or lower respiratory tract specimens, (2) the subjects could be classified into ACEI/ARB user and non-ACEI/ARB user groups, (3) the severity of disease or all-cause mortality was evaluated according to the use of ACEI/ARB and (4) any human clinical comparative study except for those with a cross-sectional design.

Information sources and search strategy

The Medline, Embase, Cochrane Central Register of Controlled Trials, MedRxiv, Social Science Research Network and Peer J databases were searched for potentially eligible published and unpublished studies up to 4 May 2020. The search strategy was designed by experienced researchers (HWL and C-HL) based on The Peer Review of Electronic Search Strategies checklist.²⁴ Manual searches were conducted for references cited in recent articles, systematic reviews and meta-analyses to complement the search strategy. When unpublished or forthcoming papers were found, we contacted the authors to obtain all available data, but none replied. There was no restriction on study period, ethnicity or language in the search strategy. The details of the search strategy are outlined in online supplemental appendix 1. The searched references from retrieved articles were imported into a reference management software (Endnote X7, Thomson Reuters, Philadelphia, Pennsylvania, USA) and shared with the other authors.

Study selection

The study selection was conducted by two individual reviewers (HWL and C-HL) based on the PRISMA flow diagram.²⁵ Duplicated studies were censored based on the study title and name of the first author. The two independent reviewers (HWL and C-HL) individually screened the titles, abstracts and keywords to select potentially eligible studies. The independent reviewers (HWL and C-HL) then conducted a full-text review to check for conformance with the prespecified eligibility criteria. In case of any conflict or disagreement, eligibility was discussed by all authors until a consensus was reached.

Data extraction and quality assessment

Data were extracted using a standardised format.²⁶ HWL and C-HL extracted data on the study characteristics (first author, published or preprinted year, region, eligibility criteria, exposure to intervention and definition of severe disease) and the baseline characteristics of the patients (number of analysed patients, age, sex and comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, pulmonary disease, cerebrovascular disease, chronic liver disease, chronic kidney disease and cancer). Two dichotomous variables (number of patients who died during the observation period and number of patients with severe disease) were used as clinical outcomes. We extracted adjusted risk ratios, including the OR and HR, when data were available. If the use of ACEI/ARB was evaluated only in the subpopulation with hypertension, the extraction process was conducted with a focus on the subpopulation, along with the collection of data for the whole population to determine any relevant differences. The risk of bias (ROB) of eligible studies was assessed using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool,²⁷ as recommended by the Cochrane Scientific Committee in 2017. If a study was assessed to have a critical level of ROB in any domain in ROBINS-I tool, a sensitivity analysis was planned after excluding the biased study.

Outcomes

The primary outcomes were all-cause mortality and severe disease. The definition of severe disease was according to individual study definitions.

Data synthesis and analysis

The outcomes were conservatively analysed using a random-effects model because heterogeneity was detected among the included studies regarding the study method and patient characteristics. Risk of all-cause mortality or severe disease events was calculated as the OR with a 95% CI in terms of summary statistics. The overall results of the meta-analysis were visualised with forest plots. The I^2 statistic and the Cochran's Q test were used to evaluate statistical heterogeneity among the effect sizes of the included studies.

Meta-regression analysis was conducted by using different variables including baseline characteristics, whether confounders were adjusted or not, and the definition of outcome, as a covariate. Subgroup analysis was also performed according to categorical covariates.

Funnel plot asymmetry and Egger's and Begg's tests were used for qualitative and quantitative evaluation of publication bias, respectively.²⁶ If publication bias was suspected, the trim-and-fill method was planned to calculate a corrected OR by estimating the number of missing studies.²⁸ All the analyses were performed using Stata software V.14.2 (StataCorp, College Station, Texas, USA), using the commands named "metan", "metafunnel", "metabias" and "metareg" and using R V.3.4.0 statistical computing software (R Foundation for Statistical Computing, Vienna, Austria) with the metafor and meta packages.²⁹ Twotailed $p < 0.05$ was considered to indicate statistical significance.

Certainty of evidence

The certainty of evidence was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.³⁰

RESULTS

Study selection

After removing duplicates, 404 studies were screened, and 35 potentially relevant articles were retrieved for full-text review (figure 1). Twenty studies met the eligibility criteria. The reasons for excluding 15 articles are described in online supplemental appendix 2. Three studies were excluded because the data could be overlapped with other included data sources.³¹ The details of data sources of included studies are described in online supplemental appendix 3. All 20 studies were observational studies, and there was no randomised controlled trial reporting relevant results. All-cause mortality was reported in 13 studies,^{13 15–17 19–21 32–37} and severe disease was reported in 13 studies.^{12–14 16–18 20 34 35 38–41} Mortality was evaluated during hospitalisation in nine studies,^{13 15–17 19 20 32 33 35} at 28 days during hospitalisation in two studies,^{21 34} during hospitalisation in about 87% of patients in one study,³⁶ and at 60 days in one study.³⁷ Severe disease was evaluated during hospitalisation in 12 studies,^{12 13 16–18 20 34 35 38–41} and during hospitalisation in severe cases in 1 study,¹⁴ where about half of mild-to-moderate cases were not hospitalised.

Baseline characteristics of the included studies and patients

The baseline characteristics of the included studies and patients are summarised in table 1 and online supplemental appendix 4. All studies were conducted in 2020; nine in China, four in the USA, three in Italy, one in Iran, one in South Korea, one in the UK and one other study across multiple countries. All the 36108 patients with a confirmed diagnosis of COVID-19 were hospitalised or isolated. Among these patients, data for 30766 patients with information on the use or non-use of ACEI/ARB were included in the meta-analysis, 8066 of whom were classified in the ACEI/ARB group. The mean age was 54.4 years and 54.5% of the included patients were men. Several comorbidities were reported, including 41.9% patients with hypertension in all 20 studies, 15.3% with cardiovascular diseases in 18 studies,

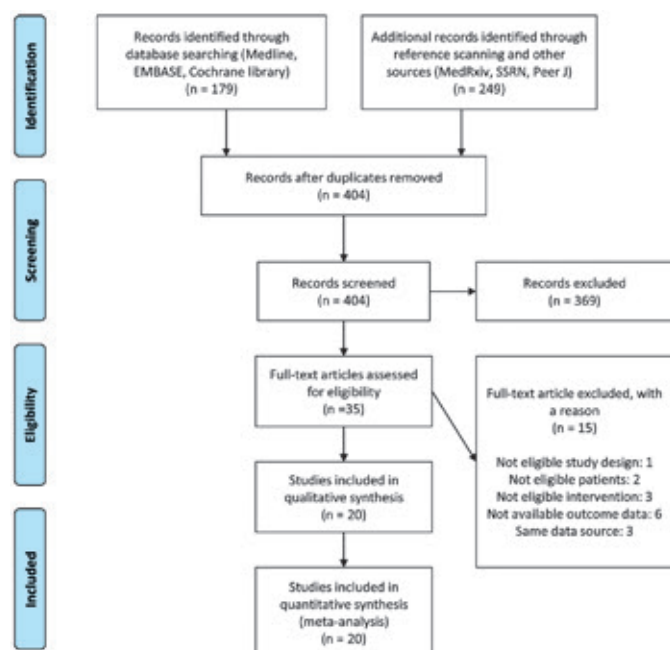


Figure 1 Preferred Reporting Items for Systematic Review and Metaanalysis (PRISMA) flow diagram for the systematic review and metaanalysis. In PRISMA flow diagram, the information of different phases of a systematic review are summarised. PRISMA flow diagram maps out the number of records identified, included and excluded, and the reasons for exclusion.

17.9% with diabetes in 17 studies, 8.8% with chronic respiratory diseases in 14 studies, 3.9% with chronic kidney disease in 12 studies, 9.1% with malignancies in 10 studies, 3.7% with cerebrovascular diseases in 8 studies and 4.6% with chronic liver diseases in 7 studies. The ACEI/ARB group was defined as those with any medication history of treatment with ACEI or ARB based on the electric medical record in 12 studies, those who used ACEI or ARB during hospitalisation in 6 studies, those who used ACEI or ARB at the time of hospitalisation in 1 study and those who were treated with ACEI or ARB within the 7 days before symptoms or during inpatient treatment in 1 study.

Definitions of severe disease followed the report of the WHO-China Joint Mission on COVID-19⁴² for (1) respiratory rate (RR) ≥ 30 , (2) O_2 saturation at rest $\leq 93\%$ and (3) PaO_2/FiO_2 ratio ≤ 300 in seven studies;^{12 13 16 17 20 38 41} the criteria for severe disease as intensive care, mechanical ventilation or death in four studies;^{14 18 39 40} the criteria for severe disease as (1) reduced consciousness, (2) RR $\geq 30/\text{min}$, (3) blood pressure $< 90/60$, (4) multilobar infiltration and (5) hypoxaemia in one study³⁵ and the severe community-acquired pneumonia definition in the clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America⁴³ in one study.³⁴

ROB assessment within studies

The ROB assessment is summarised in online supplemental appendix 5. In general, the studies had low ROB in patient selection, classification of interventions and deviations from intended interventions, but showed moderate ROB in missing data and selection bias. Many studies did not provide sufficient information on confounding variables. The majority of studies were assessed to be vulnerable to ROB in the measurement of outcomes, which was attributed to the innate nature of a retrospective study in that the outcome assessors were aware of the intervention status, rather than to a serious or critical defect in the study design.

All-cause mortality

We found 21178 patients in 11 studies reporting OR and 2 studies reporting HR. The risk of all-cause mortality was significantly decreased in the ACEI/ARB group compared with non-ACEI/ARB group with a heterogeneity (OR=0.52 (95%

CI=0.37 to 0.72), $I^2=87\%$, p value for heterogeneity < 0.01 , figure 2) (moderate level of evidence, online supplemental appendix 6). To identify factors affecting the heterogeneity, we conducted meta-regression and subgroup analyses. A metaregression analysis showed whether confounders were adjusted or not affected the effect size (test of moderator $p < 0.01$).

However, ACEI/ARB group had significantly lower risks of all-cause mortality than non-ACEI/ARB group in both subgroup analyses where confounders were adjusted (OR=0.30 (95% CI=0.22 to 0.40); $I^2=61\%$, p value for heterogeneity=0.11, figure 3) and where confounders were not adjusted (OR=0.52 (95% CI=0.37-0.72); $I^2=0\%$, p value for heterogeneity=0.59, figure 3). There were no other factors affecting the effect size in meta-regression analyses by using the following covariates: ‘including hypertensive patients only or not’ (test of moderator $p=0.92$), ‘the age of participants aged ≥ 60 or < 60 years’ (test of moderator $p=0.19$) or ‘male proportion $\geq 50\%$ or $< 50\%$ ’ (test of moderator $p=0.89$). ACEI/ARB group was associated with decreased risk of all-cause mortality in hypertensive patients only subgroup (OR=0.53 (95% CI=0.39 to 0.73); $I^2=87\%$, p value for heterogeneity=0.04, online supplemental appendix 7). ACEI/ARB group was associated with decreased risk of all-cause mortality in both subgroups of age ≥ 60 and < 60 years (online supplemental appendix 8) and was also associated with decreased risk of all-cause mortality in both subgroups of male proportion $\geq 50\%$ and $< 50\%$ (online supplemental appendix 9). The sensitivity analysis excluding three studies, in which the definition of mortality was not ‘in-hospital mortality’ but ‘28 days mortality’^{21 34} or not all patients were hospitalised,³⁶ showed a similar result (online supplemental appendix 10).

There were two studies applying HR to compare the risk of all-cause mortality between ACEI/ARB group and non-ACEI/ARB group. Because those studies included patients with largely different characteristics such as age (44.437 vs 76.0 years¹⁹), male proportion (38.5%³⁷ vs 72.3%¹⁹) and the proportion of hypertensive patients (19.0%³⁷ vs 100%),¹⁹ we did not perform a meta-analysis. Both the study by Lee *et al* (HR=1.07 (95% CI=0.66 to 1.74))³⁷ and the study by Tedeschi *et al* (HR=0.97 (95% CI=0.68 to 1.38))¹⁹ showed that ACEI/ARB use did not increase the risk of all-cause mortality compared with non-ACEI/ARB group.

Severe disease in COVID-19

For 12848 patients in 13 studies, ACEI/ARB use was not associated with an increased risk of severe disease manifestation in a meta-analysis using a random-effects model, although there was a significant heterogeneity (OR=0.68 (95% CI=0.44 to 1.07); $I^2=95\%$, p value for heterogeneity < 0.01 , figure 4) (low level of evidence, online supplemental appendix 6). We conducted a various meta-regression, but did not identify a contributor of heterogeneity among the following covariates: ‘confounders were adjusted or not’ (test of moderator $p=0.99$), ‘including hypertensive patients only or not’ (test of moderator $p=0.35$), ‘the age of participants ≥ 60 or < 60 years’ (test of moderator $p=0.21$) or ‘male proportion $\geq 50\%$ or $< 50\%$ ’ (test of moderator $p=0.58$). Whether the definition for severe disease followed the WHO-China criteria or not also did not affect the effect size (test of moderator $p=0.17$). ACEI/ARB group did not have a higher risk of severe disease than ACEI/ARB group both in subgroup of studies defining severe disease according to WHO-China criteria (OR=0.51 (95% CI=0.30 to 0.87)) and in subgroup of studies defining severe disease according to other criteria (OR=0.99 (95% CI=0.51 to 1.90)) (figure 5). ACEI/ARB was not associated with increased risk of severe disease in all other subgroup analyses, although there were statistical heterogeneities in majority of subgroup analysis (online supplemental appendices 11–14. The sensitivity analysis excluding one study,¹⁴ in which not all patients were hospitalised, showed a similar result (online supplemental appendix 15).

Table 1 Characteristics of 20 included observational studies

No.	Study	Region	Eligibility criteria	N	Age, mean	Male, %	Exposure to intervention	Definition of severe disease
1	Ashraf MA. <i>et al</i> ¹⁵	Iran	The patients confirmed with COVID-19 who were admitted to hospital	100 ACEI/ARB group: 19	58*	64.6	Medical records on ACEI or ARB was reviewed	One of the following conditions: reduced consciousness, RR ≥ 30 /min, BP $< 90/60$, Multi-lobular infiltration, hypoxaemia
2	Bean D. <i>et al</i> ¹⁹	UK	Patients with COVID-19 symptomatic and requiring inpatient admission	205 ACEI/ARB group: 46 Non-ACEI/ARB group: 60.1	63.0 ACEI/ARB group: 72.7 Non-ACEI/ARB group: 60.1	51.7 ACEI/ARB group: 54.3 Non-ACEI/ARB group: 44.6	Exposure to ACEI or ARB within 7 days before symptoms or during inpatient treatment	Death or admission to a critical care unit for organ-support within 7 days of symptoms onset
3	Benelli G. <i>et al</i> ²²	Crema, Italy	The patients diagnosed with COVID-19 who were admitted to hospital	411 ACEI/ARB group: 110	66.8	66.6	Data on medication history of ACEI or ARB was extracted from electric medical record	N/A (although CPAP/NIV use, ICU admission and death was evaluated, those outcomes can be overlapped)
4	Caraballo C. <i>et al</i> ¹⁶	USA	The adult patients (aged ≥ 18 years) with heart failure who were admitted to hospital for the treatment of confirmed COVID-19	206 ACEI/ARB group: 172	78*	45.1	Exposure to ACEI or ARB before and during hospitalisation	N/A
5	Feng Y. <i>et al</i> ¹²	Multicentre, China	All the patients diagnosed with COVID-19 who visited the hospitals designated for the treatment of COVID-19	113 (476) ACEI/ARB group: 33	(53.0)*†	(56.9)†	Data on medication history of ACEI or ARB was extracted from electric medical record	One of the following conditions: RR ≥ 30 /min, O ₂ saturation at rest $\leq 93\%$, PF ratio ≤ 300 (WHO-China criteria)
6	Feng Z. <i>et al</i> ^{18*}	Multicentre, China	All the adult patients with confirmed COVID-19 with available clinical or imaging data who were treated at hospital	65 (564) ACEI/ARB group: 16	61.5 (47)* ACEI/ARB group: 57* Non-ACEI/ARB group: 63*	50.8 (50.4) ACEI/ARB group: 62.5 Non-ACEI/ARB group: 46.9	Data on medication history of ACEI or ARB was extracted from electric medical record	One of the following conditions: RR ≥ 30 /min, O ₂ saturation at rest $\leq 93\%$, PF ratio ≤ 300 (WHO-China criteria)
7	Ip A. <i>et al</i> ²³	USA	The hypertensive patients diagnosed with COVID-19 who were admitted to hospital	1129 ACEI/ARB group: 460	–	–	Data on medication history of ACEI or ARB was extracted from electric medical record	N/A
8	Lee H. <i>et al</i> ¹⁷	South Korea	The patients diagnosed with COVID-19 who were admitted to hospital or isolated	8266 ACEI/ARB group: 977 Non-ACEI/ARB group: 64.8	44.4 ACEI/ARB group: 41.6 Non-ACEI/ARB group: 37.8	38.5 ACEI/ARB group: 56.4 Non-ACEI/ARB group: 37.8	Data on medication history of ACEI or ARB was extracted from electric medical record	N/A (severe disease was not evaluated)
9	Li J. <i>et al</i> ¹	Wuhan, China	The hypertensive patients diagnosed with COVID-19 who were admitted to hospital	362 ACEI/ARB group: 115	66* ACEI/ARB group: 65* Non-ACEI/ARB group: 67*	52.2 ACEI/ARB group: 59.1 Non-ACEI/ARB group: 49.0	Use of these drugs at the time of admission that continued through hospitalisation	One of the following conditions: RR ≥ 30 /min, O ₂ saturation at rest $\leq 93\%$, PF ratio ≤ 300 (WHO-China criteria)
10	Mancia G. <i>et al</i> ¹⁴	Italy	The beneficiaries of the Regional Health Service (aged ≥ 40 years) diagnosed with COVID-19	6272 ACEI/ARB group: 2896	68	36.7	Data on medication history of ACEI or ARB was extracted from claim data	Assisted ventilation or death
11	Mehra MR. <i>et al</i> ¹⁵	International (Asia, Europe and North America)	The patients diagnosed with COVID-19 who were admitted to hospital	8910 ACEI/ARB group: 1326	49.1	59.9	Exposure to ACEI or ARB at the time of hospitalisation	N/A
12	Meng J. <i>et al</i> ¹⁶	Shenzhen, China	The hypertensive patients diagnosed with COVID-19 who were admitted to hospital and took antihypertensive drugs	42 ACEI/ARB group: 17	62.0 ACEI/ARB group: 61.9 Non-ACEI/ARB group: 60.0	57.1 ACEI/ARB group: 47.1 Non-ACEI/ARB group: 60.0	Exposure to ACEI or ARB during hospitalisation	One of the following conditions: RR ≥ 30 /min, O ₂ saturation at rest $\leq 93\%$, PF ratio ≤ 300 (WHO-China criteria)
13	Peng Y. <i>et al</i> ¹⁷	Wuhan, China	The adult patients (aged ≥ 18 years) with cardiovascular disease who were diagnosed with COVID-19 and treated in hospital. The patients with systemic diseases, liver disease or kidney abnormalities were excluded	112 ACEI/ARB group: 22	62.0	47.3	Data on medication history of ACEI or ARB was extracted from electric medical record	One of the following conditions: RR ≥ 30 /min, O ₂ saturation at rest $\leq 93\%$, PF ratio ≤ 300 (WHO-China criteria)
14	Rentsch CT. <i>et al</i> ¹⁰	USA	Among the eligible patients in VA who underwent COVID-19 tests, only patients with a positive test for COVID-19 were evaluated in our study	585 ACEI/ARB group: 255	66.1	95.5	Data on medication history of ACEI or ARB was extracted from electric medical record	Intensive care
15	Reynolds HR. <i>et al</i> ¹⁸	USA	Propensity score-matched patients with a positive test for COVID-19	2211 (5894) ACEI/ARB group: 1110	–†	–†	Data on medication history of ACEI or ARB was extracted from claim data	Admission to the intensive care unit, the use of non-invasive or invasive mechanical ventilation or death
16	Tedeschi S. <i>et al</i> ¹⁹	Italy	Prospectively enrolled adult patients with hypertension who were hospitalised and diagnosed with a microbiologically confirmed COVID-19	311 ACEI/ARB group: 175	76*	72.3	Patients received antihypertensive medication including ACEI or ARB during hospitalisation	N/A

Continued

Table 1 Continued

No.	Study	Region	Eligibility criteria	N	Age, mean	Male, %	Exposure to intervention	Definition of severe disease
17	Yan H. <i>et al</i> [†]	Zhejiang, China	All adult patients diagnosed with COVID-19	All adult patients diagnosed with COVID-19	(48.8) [†]	(51.1) [†]	Data on medication history of ACEI or ARB was extracted from electronic medical record	One of the following conditions: RR ≥ 30 /min, O ₂ saturation at rest $\leq 93\%$, PF ratio ≤ 300 , respiratory failure requiring mechanical ventilation, shock and requiring ICU admission requirement due to multiple organ failure (WHO-China criteria)
18	Yang G. <i>et al</i> [†]	Wuhan, China	The patients diagnosed with COVID-19 who were admitted to hospital	126 (251) ACEI/ARB group: 43 Non-ACEI/ARB group: 67*	66 (66)* ACEI/ARB group: 65* Non-ACEI/ARB group: 67*	49.2 (49.0) ACEI/ARB group: 48.8 Non-ACEI/ARB group: 49.4	Exposure to ACEI or ARB prior to admission and during hospital stay	One of the following conditions: RR ≥ 30 min, O ₂ saturation at rest $\leq 93\%$, PF ratio ≤ 300 (WHO-China criteria)
19	Zeng Z. <i>et al</i> [†]	Wuhan, China	The hospitalised patients suspected and confirmed of patients with COVID-19 who were aged ≤ 18 years, whose entire stay in hospital lasted for < 48 hours were excluded	75 (274) ACEI/ARB group: 28 Non-ACEI/ARB group: 69	67 (60) ACEI/ARB group: 64 Non-ACEI/ARB group: 69	46.7 (54.7) ACEI/ARB group: 42.9 Non-ACEI/ARB group: 48.9	Data on medication history of ACEI or ARB was extracted from electronic medical record	One of the following conditions: septic shock, mechanical ventilation Three of the following conditions: RR ≥ 30 /min, PF ratio ≤ 250 , multiple infiltration, altered mentality, BUN ≥ 20 mg/dL, WBC < 4000 cells/ μ L, platelet < 100 000/ μ L, body temperature $< 36^\circ\text{C}$, hypotension requiring fluid resuscitation (ATIS/IDSA criteria for severe pneumonia)
20	Zhang P. <i>et al</i> [†]	Multicentre, China	The hypertensive adults (aged 18–74 years) diagnosed with COVID-19 who were admitted to hospital. The patients with incomplete medical records, pregnancy, lethal organ injury, decompensated or end-stage disease, AIDS or malignancy were excluded	1128 ACEI/ARB group: 188 Non-ACEI/ARB group: 64	64* ACEI/ARB group: 64 Non-ACEI/ARB group: 64	53.5 ACEI/ARB group: 53.2 Non-ACEI/ARB group: 53.5	Exposure to ACEI or ARB during hospitalisation	N/A (although acute respiratory syndrome, septic shock, disseminated intravascular coagulopathy and acute kidney injury were evaluated, those outcomes can be overlapped)

Some studies evaluated the association between ACEI/ARB use and severe disease or mortality only in the subgroup patients with hypertension. If the information is available, we described the information of hypertensive patients first, and then the information of all patients in the bracket.

*Only median value was reported.

†Only the values of the whole patient cohort were available; the values of the subjects analysed in the study were not presented.

ACEI, ACE inhibitor; ARB, angiotensin II receptor antagonist; ATIS, American Thoracic Society; BP, blood pressure; BUN, blood urea nitrogen; IDSA, Infectious Diseases Society of America; N/A, not available; NIV, non-invasive ventilation; PF, ratio; PaO₂/FIO₂, RR, respiratory ratio; WBC, white blood cell.

Publication bias

Observation of funnel plots supported by Egger's and Begg's tests indicated no significant publication bias for the associations with mortality and severe disease (online supplemental appendix 16).

DISCUSSION

To our knowledge, this is the systematic review and metaanalysis investigating the association between ACEI/ARB treatment and the risk of mortality and severe disease in patients with COVID-19 first registered in PROSPERO. ACEI/ARB use was significantly associated with a decreased risk of all-cause mortality in meta-analysis for studies using ORs. Two studies using HR did not show an increased risk of all-cause mortality in ACEI/ARB group compared with non-ACEI/ARB group. Thus, we concluded that ACEI/ARB did not increase the risk of all-cause mortality in patients infected with SARS-CoV-2. ACEI/ARB use was not associated with an increased risk of severe disease, although there was a significant heterogeneity. We rated moderate certainty of evidence for all-cause mortality and low certainty of evidence for severe disease, mainly rated down due to the limitation of retrospective study design. Overall, the continuation of ACEI/ARB use during the COVID-19 pandemic can be a suitable strategy as current guidance suggested.¹¹

Hypertension, cardiovascular diseases and diabetes are the most common comorbidities of patients with severe disease in COVID-19,⁴⁴ which are commonly treated with ACEI/ARBs. Researchers have postulated that ACEI/ARB use could be a link between more frequent cases of severe disease symptoms in patients with comorbidities.^{44–47} This is based on the fact that ACEI/ARBs were found to upregulate ACE2 expression in rats and human intestinal cells.^{2–4} Since ACE2 is the receptor for SARS-CoV-2 entry in the host cell,^{5,6} ACEI/ARB use could facilitate worse symptoms in patients with COVID-19.^{44–47}

However, our study does not support this speculation; it even suggests a potential benefit of ACEI/ARB for some COVID-19 patients given that a decreased risk of all-cause mortality was observed in the meta-analysis for studies using ORs. The biological mechanism of these beneficial effects with ACEI/ARB could be explained from two perspectives.⁴⁸ First, ACEI/ARBs inhibit the activity of angiotensin II, which increases blood pressure, retention of sodium and water,⁴⁹ inflammation⁵⁰ and tissue injury.⁵¹ Thus, these drugs attenuate lung and cardiovascular insults, which could prevent severe disease and death.⁵² In fact, serum angiotensin II levels were found to be markedly elevated and linearly associated with viral load and lung injury in patients with COVID-19.⁵³ Second, ACEI/ARBs upregulate ACE2, which is expressed in the heart, lung, intestine and kidneys.⁵⁴ Human coronaviruses downregulate ACE2 expression on cell membranes after invading cells,^{55,56} thereby enhancing neutrophil infiltration in the lungs.⁵⁷ Since angiotensin II is the main substrate of ACE2, the increase in ACE2 levels by ACEI/ARBs could mitigate the harmful effects of angiotensin II. ACE2 also degrades angiotensin I to angiotensin-(1-9), inducing anti-inflammatory, antioxidative and vasodilating effects through binding to the Mas receptor.¹¹ In fact, some previous studies suggested that ACEI/ARBs may have a beneficial effect in preventing pneumonia^{58,59} and in improving the outcomes of patients with acute respiratory distress syndrome.⁶⁰ The study of Meng *et al*,¹⁶ which was included in our meta-analysis, demonstrated no difference in viral load at baseline, although the peak viral load was significantly lower in the ACEI/ARB group than in the non-ACEI/ARB group ($p=0.03$).

Our study has limitations. First, the interpretation of the results from our systematic review and meta-analysis should be careful because of high ROB from observational studies. According to GRADE approach, we attenuated the certainty of our conclusions. Second, the definition of severe disease was

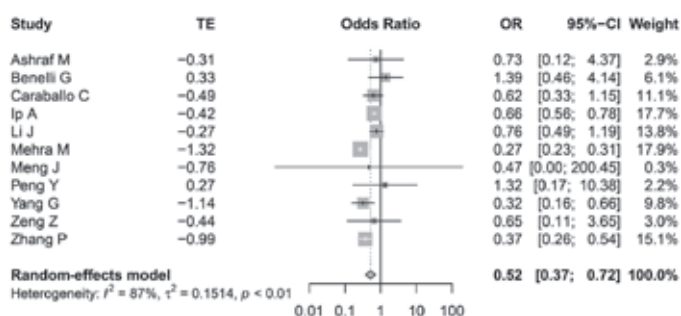


Figure 2 Forest plot for all-cause mortality using OR. All-cause mortality data of OR and 95% CI from 11 studies were pooled in this meta-analysis using random-effects model and the result of metaanalysis was described as a forest plot. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond on the bottom of this forest plot indicated a pooled OR and 95% CI. TE, treatment effect.

heterogeneous among studies. Seven studies defined severe disease based on the WHO-China criteria, and six studies used other different criteria.

The heterogeneous definition for severe disease may have led to a significant statistical heterogeneity in the meta-analysis ($I^2=91\%$, p value for heterogeneity <0.01). Although ACEI/ARB group did not increase the risk of severe disease both in subgroup of studies defining severe disease according to WHO-China criteria and in subgroup of those using other criteria, the results should be cautiously interpreted considering the heterogeneity of outcome definition and the statistical heterogeneity. Third, there were a little bit different time points when the outcomes were evaluated. Most studies evaluated severe disease and mortality during hospitalisation. However, in the study by Mancía et al, half of patients with non-severe disease were not hospitalised, although all patients with severe disease were hospitalised. In the study by Caraballo *et al*, about 87% of patients with COVID-19 were hospitalised and in-hospital mortality was evaluated. We postulated the patients with COVID-19 who were not hospitalised as those with mild disease who recovered spontaneously without hospitalisation. The studies by Zeng *et al* and Zhang *et al* used 28 days mortality. However, we performed sensitivity analysis, excluding those studies, which showed similar results. Fourth, we found significant interstudy heterogeneities in meta-analyses for all-cause mortality and severe disease. To identify factors contributing on interstudy heterogeneity, we conducted metaregression analysis and subgroup analysis. We

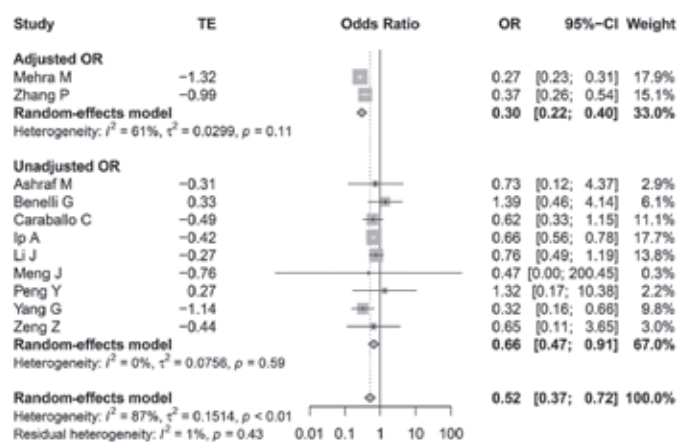


Figure 3 Forest plot for all-cause mortality in adjusted OR and unadjusted OR. Subgroup analysis for all-cause mortality was conducted according to adjusted or unadjusted OR. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond of this forest plot indicated a pooled OR and 95% CI in each subgroup analysis and in overall population. Meta-regression analysis performed using 'unadjusted versus adjusted' as the covariate affected the effect size (test of moderator, $p < 0.001$). TE, treatment effect.

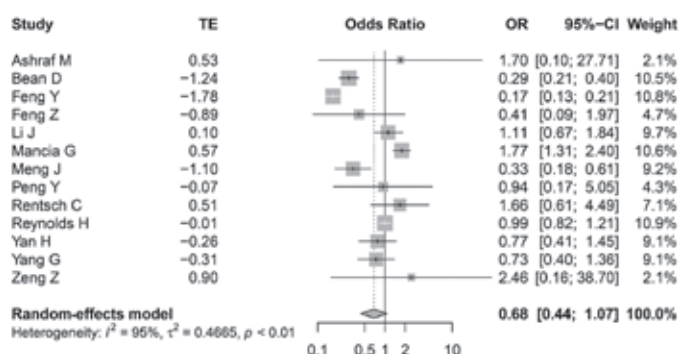


Figure 4 Forest plot for severe disease using OR. Severe disease data of OR and 95% CI from 13 studies were pooled in this meta-analysis using random-effects model and the result of meta-analysis was described as a forest plot. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond on the bottom of this forest plot indicated a pooled OR and 95% CI. TE, treatment effect.

identified whether confounders were adjusted or not significantly affect the effect size for all-cause mortality and conducted subgroup analysis according to confounders were adjusted or not. However, both subgroup analysis showed that ACEI/ARB group did not have a higher risk of all-cause mortality than non-ACEI/ARB group as described above. Fifth, although all the included studies fulfil the eligibility criteria stipulated in the present systematic review, there were several inconsistent participant criteria because of eligible age (all adults vs ≥ 40 years old), comorbidities (general population vs specific disease cohort) and indications to exclude specific comorbid diseases.

CONCLUSIONS

The ACEI/ARB treatment does not increase the risk of all-cause mortality in patients with COVID-19. ACEI/ARB use does not increase the risk of severe disease, although the heterogeneous outcome definition and the statistical heterogeneity should be considered. Physicians can prescribe ACEI/ARB without concern of drug-related worsening in patients with COVID-19.

Contributors Study concept and design: HWL and C-HL. Acquisition of data: HWL and C-HL. Analysis and interpretation of data: HWL and C-HL. Manuscript drafting: HWL and C-HL. Critical revision of the manuscript and important intellectual content: EJJ and C-HY. Study supervision: C-HL.

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Competing interests None declared.

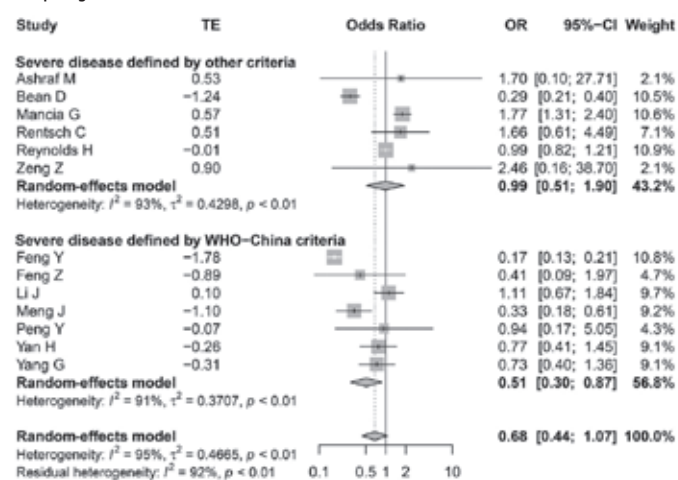


Figure 5 Forest plot for severe disease according to the definition of severe disease. Subgroup analysis for severe disease was conducted according to whether the definition of severe disease followed WHOChina criteria or not. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond of this forest plot indicated a pooled OR and 95% CI in each subgroup analysis and in overall population. Metaregression analysis performed using 'defined by WHO-China criteria versus other criteria' as the covariate did not affect the effect size (test of moderator, $p = 0.1657$). TE, treatment effect.

Patient consent for publication Not required.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The data are available by accessing the published studies listed in table 1.

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REFERENCES

- World Health Organization. Overview of coronavirus (COVID-19), 2020. Available: <https://covid19.who.int/> [Accessed 24 Apr 2020].
- Ishiyama Y, Gallagher PE, Averill DB, et al. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* 2004;43:970–6.
- Klimas J, Olvedy M, Ochodnicka-Mackovicova K, et al. Perinatally administered losartan augments renal ACE2 expression but not cardiac or renal MAS receptor in spontaneously hypertensive rats. *J Cell Mol Med* 2015;19:1965–74.
- Vuille-dit-Bille RN, Camargo SM, Emmenegger L, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. *Amino Acids* 2015;47:693–705.
- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.
- Wan Y, Shang J, Graham R, et al. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020;94. doi:10.1128/JVI.00127-20. [Epub ahead of print: 17 Mar 2020].
- Zheng YY, YT M, Zhang JY, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020.
- Kissler SM, Tedijanto C, Goldstein E, et al. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science* 2020;368:860–8.
- Shah SJ, Stafford RN. Current trends of hypertension treatment in the United States. *Am J Hypertens* 2017;30:1008–14.
- Kim SH, Shin DW, Kim S, et al. Prescribing patterns of antihypertensives for treatment-naïve patients in South Korea: from Korean NHIS claim data. *Int J Hypertens* 2019;2019:1–10.
- Bavishi C, Maddox TM, Messerli FH, et al. COVID-19 infection and renin-angiotensin system blockers. *JAMA Cardiol* 2019.
- Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med* 2020;201:1380–8.
- Li J, Wang X, Chen J, et al. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 2020;5:825.
- Mancia G, Rea F, Ludergnani M, et al. Renin-Angiotensin-Aldosterone system blockers and the risk of Covid-19. *N Engl J Med* 2020.
- Mehra MR, Desai SS, Kuy S, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med* 2020.
- Meng J, Xiao G, Zhang J, et al. Renin-Angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020;9:757–60.
- Peng Y, Meng K, Guan H, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. *2020;48:E004–E04*.
- Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone system inhibitors and risk of Covid-19. *N Engl J Med* 2020.
- Tedeschi S, Giannella M, Bartoletti M, et al. Clinical impact of renin-angiotensin system inhibitors on in-hospital mortality of patients with hypertension hospitalized for coronavirus disease 2019. *Clin Infect Dis* 2020;71:899–901.
- Yang G, Tan Z, Zhou L, et al. Effects of ARBs and ACEIs on virus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study. *Hypertension* 2020.
- Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;126:1671–81.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-Analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (moose) group. *JAMA* 2000;283:2008–12.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;75:40–6.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- Higgins JP, Green S. *Cochrane Handbook for systematic reviews of interventions* version 5.1.0. The cochrane collaboration 2011.
- Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
- Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
- Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw* 2010;36:1–48.
- Guyatt GH, Oxman AD, Vist GE, et al. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- Bauchner H, Golub RM, Zylke J. Editorial Concern—Possible reporting of the same patients with COVID-19 in different reports. *JAMA* 2020;323:1256.
- Benelli G, Buscarini E, Canetta C, et al. SARS-CoV-2 comorbidity network and outcome in hospitalized patients in Crema, Italy 2020.
- Ip A, Parikh K, Parrillo JE, et al. Hypertension and renin-angiotensin-aldosterone system inhibitors in patients with Covid-19 2020.
- Zeng Z, Sha T, Zhang Y, et al. Hypertension in patients hospitalized with COVID-19 in Wuhan, China: A single-center retrospective observational study, 2020.
- Ashraf MA, Shokouhi N, Shirali E, et al. COVID-19 in Iran: a comprehensive investigation from exposure to treatment outcomes 2020.
- Caraballo C, McCullough M, Fuery M, et al. COVID-19 infections and outcomes in a live registry of heart failure patients across an integrated health care system. *medRxiv* 2020.
- Lee H-Y, Ahn J, Kang CK, et al. Association of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors on COVID-19-Related outcome. *SSRN Journal* 2020.
- Feng Z, Li J, Yao S, et al. The use of adjuvant therapy in preventing progression to severe pneumonia in patients with coronavirus disease 2019: a multicenter data analysis 2020.
- Bean D, Kraljevic Z, Searle T, et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-CoV-19 infection in a multi-site UK acute Hospital trust 2020.
- Rentsch CT, Kidwai-Khan F, Tate JP, et al. Covid-19 testing, hospital admission, and intensive care among 2,026,227 United States veterans aged 54-75 years 2020.
- Yan H, Valdes AM, Vijay A, et al. Role of drugs affecting the renin-angiotensin-aldosterone system on susceptibility and severity of COVID-19: a large case-control study from Zhejiang Province, China. *medRxiv* 2020.
- World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19) 2020.
- Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic Society and infectious diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45–67.
- Guan WJ, ZY N, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020.
- Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020;8:e21.
- Fang L, Karakiulakis G, Roth M. Antihypertensive drugs and risk of COVID-19? - Authors' reply. *Lancet Respir Med* 2020.
- Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. *J Travel Med* 2020;27.
- Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020;81:537–40.
- Brewster UC, Perazella MA. The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. *Am J Med* 2004;116:263–72.
- Marchesi C, Paradis P, Schiffrin EL. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci* 2008;29:367–74.
- Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol* 2007;7:803–15.
- Vaduganathan M, Vardeny O, Michel T, et al. Renin-Angiotensin-Aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020.
- Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020;63:364–74.
- Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7.
- Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;11:875–9.
- Dijkman R, Jebbink MF, Deijs M, et al. Replication-Dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. *J Gen Virol* 2012;93:1924–9.
- Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg9 bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. *Am J Physiol Lung Cell Mol Physiol* 2018;314:L17–31.
- Caldeira D, Alarcão J, Vaz-Carneiro A, et al. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ* 2012;345:e4260.
- Kim J, Lee J-K, Heo EY, et al. The association of renin-angiotensin system blockades and pneumonia requiring admission in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:2159–66.
- Kim J, Choi SM, Lee J, et al. Effect of renin-angiotensin system blockade in patients with acute respiratory distress syndrome: a retrospective case control study. *Korean J Crit Care Med* 2017;32:154–63.



INSPIRA ESTABILIDADE¹ EXPIRA CONFIANÇA²



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

O primeiro fôlego na DPOC.¹



LABA (LABA)



LAMA (LAMA)



LAMA (LAMA)

Laventair
umeclidínio + vilanterol ELLIPTA
ELE PROTEGE

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

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

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

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM

▼ Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas para <http://www.infarmed.pt/web/infarmed/submissao> e para o departamento médico da GlaxoSmithKline para lis.nucleo-farmacovigilancia@gsk.com.

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

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INNOVIVA



Bial
Keeping life
in mind.

ARTIGO ORIGINAL INVESTIGAÇÃO

Tabagismo das avós, asma e função pulmonar nas crianças: estudo de coorte *Lifelines*Gillian M Mahon,¹ Gerard H Koppelman,¹ Judith M Vonk²

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¹Department of Pediatric Pulmonology and Pediatric Allergy, GRIAC Research Institute, University Medical Center Groningen Beatrix Children's Hospital, Groningen, The Netherlands

²Department of Epidemiology, GRIAC Research Institute, University Medical Center Groningen, Groningen, The Netherlands

Correspondence to

Dr Judith M Vonk, Department of Epidemiology, GRIAC research institute, University Medical Centre Groningen, Groningen, The Netherlands; j.m.vonk@umcg.nl

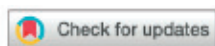
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RESUMO

Contexto/objetivo Existe pouca investigação sobre a associação entre o tabagismo das avós durante a gravidez e o risco de asma e função pulmonar alterada nos netos. Este estudo procurou investigar esta associação num âmbito de três gerações.

Métodos 37 291 participantes (25 747 adultos e 11 544 crianças) foram incluídos no estudo *Lifelines*, um estudo de coorte prospetivo longitudinal de três gerações nos Países Baixos. A espirometria foi realizada em 69,5% dos adultos e 61,1% das crianças incluídas no estudo. Utilizou-se a regressão logística e linear para analisar a associação entre o tabagismo das avós durante a gravidez e (1) asma, (2) asma infantil precoce (ou seja, início antes dos 6 anos) e (3) nível de função pulmonar. O tabagismo das avós maternas e paternas foram estudados separadamente e as análises foram estratificadas por adulto/criança e sexo. As análises foram ajustadas por sexo, tabagismo atual, variáveis de nascimento e estatuto socioeconómico.

Resultados Na população adulta, o tabagismo das avós maternas durante a gravidez foi associado a um risco mais elevado de asma (OR (95% IC): 1,38 (1,06 a 1,79)), asma de início precoce na infância (1,49 (95% IC) 1,06 a 2,11) e um FEV₁/FVC% previsto mais reduzido (B (95% IC): -1,04 (-1,91 a -0,16)) nos homens. Estes resultados não foram observados numa análise separada das crianças que participaram neste estudo. Também não se verificou uma associação significativa entre o tabagismo da avó paterna e a asma/função pulmonar.

Conclusão O tabagismo nas avós maternas durante a gravidez está associado a um risco acrescido de asma e a uma menor função pulmonar nos netos masculinos e a um efeito inverso nos netos masculinos das gerações seguintes. O nosso estudo destaca os efeitos profundamente enraizados do tabagismo ao longo das gerações.

INTRODUCTION

Asthma is a highly prevalent disease reported to affect more than 358 million people worldwide in 2015.¹ In utero exposure to tobacco smoke is a long identified risk factor not only for asthma, but also for childhood respiratory symptoms and lower lung function in the first generation offspring.²

In the Netherlands, a peak in the prevalence of women smoking was observed in 1970 (42%), which steadily decreased in 1990 (32%) and further decreased in 2017 (14.1%).³ It is difficult to define the historical trends of women smoking specifically during pregnancy, however it was reported that 46% of Dutch women of childbearing age (20 to 34 years) smoked in 1958.⁴ More recently in 2010, one-third of Dutch women smokers (6.3% of women) reported to have smoked during pregnancy exposing more than 11 000 fetuses per year.⁵

Key messages

What is the key question?

- To investigate the effect of tobacco smoking during pregnancy on the risk for asthma and lung function in second generation offspring.

What is the bottom line?

- Grandmaternal smoking during pregnancy is associated with a higher asthma risk and lower lung function in male grandchildren.

Why read on?

- The adverse effects of tobacco smoking are deeply rooted across generations and this awareness in clinical practice contributes to promoting life-long respiratory health.

In experimental animal studies, the effects of smoking on respiratory health are not only seen in the directly exposed fetus but also in the indirectly exposed gametes that form the second generation offspring. Exposing pregnant rats to subcutaneous nicotine was associated with lung function decrements and male specific increased airway hyperresponsiveness to methacholine in both first (F1) and second (F2) generation offspring.⁶ In a more recent study, adult mice were exposed pre-conception and post-conception to secondhand cigarette smoke. An altered lung integrity and a higher incidence of allergic asthma was found in both F1 and F2 progeny compared with comparable progeny of adult mice exposed to filtered air.⁷ These studies raise the question whether the smoking-induced epigenetic traits, that are associated with asthma risk and/or the level of lung function, exercise intergenerational effects via the germ line.

While many human studies show the effect of smoking during pregnancy on F1 offspring,⁸ few and somewhat conflicting studies have assessed the intergenerational inheritance patterns seen in the F2 generation in animal models. One of the first human studies observed a higher risk for childhood asthma, specifically early childhood asthma, when maternal grandmothers smoked while pregnant. This risk was independent of maternal smoking.⁹ In 2014, Miller *et al* were unable to replicate these findings for maternal grandmaternal smoking; however they found a higher risk for childhood asthma in granddaughters when investigating the effect of paternal grandmaternal smoking during pregnancy.¹⁰ This paternal specific association was found insignifi-

cant in another more recent study.¹¹ Further to this, two large Scandinavian studies investigated the risk of asthma outcomes in grandchildren as a result of maternal/grandmaternal smoking during pregnancy. One study found an associated higher risk for asthma symptoms and medication usage at ages 36 months and 7 years¹² while a more recent study found an associated higher prevalence of childhood wheeze and use of asthma medications.¹³ Maternal smoking is also known to be associated with a lower lung function in F1 offspring.^{14,15} However, only one study in humans investigated the effect of grandmaternal smoking during pregnancy on lung function in the F2 generation and no significant associations were found.¹⁰ Thus, when assessing the intergenerational effects of smoke exposure, research should account for gender specific effects, timing of symptoms (ie, early onset asthma vs later onset asthma), as well as potential smoking effects on lung function in the grandchildren.

The aim of this study was to investigate the association between grandmaternal smoking during pregnancy and asthma, early childhood asthma and lung function levels (FEV₁, FVC and FEV₁/FVC ratio) in grandchildren using the three generation Lifelines cohort study. We separately analysed early childhood asthma since previous studies showed that this phenotype seems to be most affected by grandmaternal smoking during pregnancy. Stringent criteria were used to define asthma specifically, in order to avoid the inclusion of non-asthmatic childhood wheeze; moreover, we investigated a population comprised of grandchildren with an extensive age range (4 years old to 50 years old) over a long time period (pregnancies between 1967 to 2013) which incorporated different trends in smoking prevalence. The role of gender was scrutinised by separately analysing paternal and maternal grandmaternal smoking and outcomes in both grandsons and granddaughters.

MATERIALS AND METHODOLOGY

Study population

The data used in these analyses were collected as part of the prospective population based Lifelines cohort study which investigates 167 548 subjects from three northern provinces of The Netherlands.¹⁶ The Lifelines study was founded to facilitate research on chronic disease and healthy ageing and follows participants aged between 6 months and 93 years who were enrolled between 2006 and 2013.¹⁷ Subjects aged between 25 and 50 years were initially invited to participate via their general practitioner. Subsequently, family members of the participants (parents, partners and children) were also asked to participate resulting in the inclusion of two-generation or three-generation families. At baseline examinations, participants completed a questionnaire and had several clinical measurements including lung function. All participants were followed up by means of a questionnaire every 1.5 years and extensive physical examination every 5 years.¹⁷ All participants signed a written informed consent.

The questionnaires used in the Lifelines' cohort differed for children (age <18 years) and adults. We therefore analysed children and adults separately. In both groups, grandchildren (F2) can be distinguished. For the F2 generation/grandchildren, we required the participation of at least one parent (F1) as these subjects report the smoking habits of the grandmothers during pregnancy (F0). Therefore, as figure 1 illustrates, the F1 generation in the children group can also be included as the F2 generation in the adult group. Unfortunately, detailed pedigree information and genetic profiles were not available and therefore we could not adjust for multiple (grand)children of the same (grand)mother.

In our analyses, children younger than 4 years of age (n=2411) were not included. This was due to the style of this first questionnaire where parents were asked to retrospectively report on asthma in their child before the age of 4 and as a result, data was either incomplete or missing because these children had not reached the age of 4. Also, adults older than 50 years (n=42 555) were

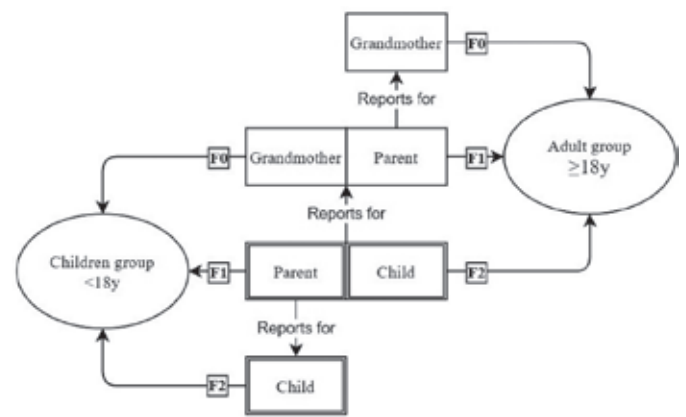


Figure 1 The different representation of three generations in both adult and children group and the roles of these generations in reporting information. F0, grandmaternal variables, for example, grandmaternal smoking; F1, maternal/paternal variables, for example, maternal smoking; F2, child variables, for example, asthma.

excluded from our analysis since the parents of these subjects were not included in the cohort and therefore, data on grandmaternal smoking was not available. We conducted our analysis on the remaining population consisting of 122 582 participants.

Outcome variables

Variables for the children and the adult group were defined separately. The questionnaires were completed by the parents in the children group and by the participants themselves in the adult group. These variables were defined within the constraints of the questionnaires. Asthma in the adult group was defined if one of the following two criteria was present: (1) Doctor diagnosed asthma ever or (2) At least two symptoms (wheeze, shortness of breath at rest, nocturnal shortness of breath based on the European Community Respiratory Health Survey-questionnaire (www.ecrhs.org)) and current use of at least one medication (β -agonist, long acting β -agonist/inhaled corticosteroid combination therapy, inhaled corticosteroid, anti-cholinergic, cromoglycate, theophylline, leukotriene receptor antagonist). If participants reported to have never been diagnosed with asthma nor having received treatment for asthma, they were included in the 'no asthma' group. Asthma in the children group was defined as ever having received treatment for asthma by a doctor. Participants who did not were included in the 'no asthma' group. We defined two asthma outcomes namely asthma and early childhood asthma. Asthma was the total group of those with asthma irrespective of age of onset. We defined early childhood asthma as having the first asthma attack before the age of 6 years. Pulmonary function was measured by trained Lifelines assistants with spirometry according to ATS (American Thoracic Society) guidelines using Welch Allyn V.1.6.0.489, PC-based SpiroPerfect with CardioPerfect Workstation software. A completed pulmonary function measurement consists of at least three technically correct manoeuvres. Spirometry was not performed in children younger than 8 years. Due to time constraints spirometry was performed in 70% of the participants. The subjects without lung function data were excluded from the analysis. The reference values of the Global Lung Function Initiative¹⁸ were used to calculate the % predicted values. We evaluated lung function based on the following measurements: FEV₁/FVC ratio, FEV₁ and FVC.

Grandmaternal and maternal smoking variables

Grandmaternal smoking in both children and adults was defined if their mother and/or father reported that either the grandmother continued smoking as usual during pregnancy, smoked less or quit during (and not before) pregnancy. Smoking dose was not accounted for. In cases where smoking stopped before pregnancy, grandmaternal smoking was not assumed. Information on grandpaternal smoking was not included in the

questionnaires. Maternal smoking in the adult group was defined if either of the following was reported: Mother continued smoking as usual during pregnancy, smoked less or quit during pregnancy. In the children group, maternal smoking was identified as present if the mother smoked during 1 to 3 or 3 to 6 or 6 to 9 months of the pregnancy. Absence of maternal smoking during pregnancy was specifically reported.

Confounding variables

We adjusted our analyses for the following smoke exposure variables: maternal smoking during pregnancy, current smoking, former smoking and environmental smoke exposure in childhood. Birth variables were also adjusted for by including maternal age, birth weight, gestational age and history of breast feeding. We also adjusted for socioeconomic status (SES) and we defined this variable according to previous Lifelines associated research using income and education variables.¹⁹ Income was defined as net monthly household income and categorised into five earning brackets. Education was measured according to The Dutch Standard Classification of Education (SOI) and was categorised into four levels. For children we used the highest income and education of the parents. To avoid missing data in our covariates we recoded all missing values into an 'unknown' category.

Statistical analysis

We conducted analysis using logistic regression where the primary outcomes were asthma and early childhood asthma and the predictor variable was grandmaternal smoking during pregnancy. Maternal grandmaternal smoking and paternal grandmaternal smoking were analysed separately. We used linear regression to analyse the association between grandmaternal smoking during pregnancy and lung function levels (expressed as % of predicted). Given the time trends of maternal smoking during pregnancy (low prevalence before 1950, followed by a gradual increase with the maximum prevalence around 1970) and in early childhood asthma/asthma (gradual increase in prevalence after the 1960s) we did not adjust for age since this may lead to over adjustment. We adjusted for gender, smoking exposure, birth variables and SES. The analysis was performed separately for children and adults due to different variable definitions. We also stratified the analyses by gender and by maternal smoking during pregnancy. A two-sided p value <0.05 was considered statistically significant. The analyses were performed using SPSS.²⁰

RESULTS

Of the 122 582 participants, we included 37 291 participants (11 544 children and 25 747 adults) who provided information on either maternal grandmaternal smoking and/or paternal grandmaternal smoking. (see figure 2) This reduction in data was due to the necessity of participation of multiple generations to determine grandmaternal smoking during pregnancy. The full comparison of the included and not included groups can be seen in the online supplement of this article (online supplemental table S1). Those included in the analyses were younger than those not included. They also had a higher prevalence of asthma particularly early childhood asthma and a lower prevalence of maternal smoking and childhood exposure to passive smoking compared with subjects not included in the analyses. Finally, the included subjects had a lower prevalence of current smoking, a higher mean birth weight and a higher prevalence of being breast fed than the not included subjects.

Table 1 outlines the characteristics of the included study population. The prevalence of asthma in both children and adult groups was comparable (11%) while a higher prevalence of early childhood asthma (<6 years) in the children group was observed (9.3% vs 4.4%). Maternal and paternal grandmaternal smoking during pregnancy was more prevalent in the children group while maternal smoking during pregnancy was more prevalent in the adult group.

In the adult group, maternal grandmaternal smoking was associated with a higher risk for both asthma and early childhood asthma (table 2). This higher risk was specifically observed in male grandchildren (asthma OR (95% CI): 1.38 (1.06 to 1.79) and early childhood asthma OR (95% CI): 1.49 (1.06 to 2.11)). When taking maternal smoking during pregnancy into account, a higher risk for early childhood asthma was present in the adult offspring of non-smoking mothers (OR (95% CI): 1.51 (1.12 to 2.05)), however, with adjustment this association was no longer significant probably due to lower sample size. There was no significant association between paternal grandmaternal smoking and any asthma outcomes (online supplemental table S2).

In the children group, a higher risk for asthma or early childhood asthma was not observed in the total group but instead a lower risk was seen in male grandchildren who were exposed to maternal grandmaternal smoking during pregnancy.

In both adults and children, there was no significant association between grandmaternal smoking and FEV₁/FVC % predicted in the grandchildren. In the stratified analyses in the adult group, maternal grandmaternal smoking was associated with a lower FEV₁/FVC % predicted in male grandchildren as well as in offspring of smoking mothers (table 3). In children, grandmaternal smoking was associated with a higher FEV₁ % predicted and FVC % predicted in male grandchildren and with a higher FVC % predicted in grandchildren with non-smoking mothers (online supplemental table S3).

DISCUSSION

In this large population-based study in The Netherlands, the effects of maternal grandmaternal smoking during pregnancy on risk for childhood asthma differ between age-groups and therefore, time-periods. In the analysed adult group, maternal grandmaternal smoking during pregnancy was associated with a higher risk for both asthma and early childhood asthma in grandchildren. This risk for both asthma outcomes was consistently significant in grandsons while granddaughters only had a higher risk for early childhood asthma which attenuated with adjustment. Additionally, the risk for early childhood asthma was only seen in children of non-smoking mothers. In contrast, in the separately analysed children group, maternal grandmaternal smoking during pregnancy was associated with a lower risk for both asthma and early childhood asthma specifically in grandsons. Paternal grandmaternal smoking during pregnancy was not associated with any risk for asthma or early childhood asthma. For lung function, we found that maternal grandmaternal smoking during pregnancy was related to a lower FEV₁/FVC % predicted in grandsons and in subjects with smoking mothers in the adult group. In the children group, grandmaternal smoking during pregnancy was associated with higher FEV₁ % predicted and FVC % predicted in grandsons.

There are two main remarkable outcomes of this research. The first is the different outcomes observed between the two different groups, adults and children. The second is the profound male predominance, where asthma risk and lung function of male grandchildren are more significantly affected by grandmaternal smoking during pregnancy than that of female counterparts. Grandmaternal smoking during pregnancy seemed to exert a detrimental effect in those grandchildren of older generations (adult group), born approximately before the 1990s in this study, as these grandchildren had a higher risk for asthma and early childhood asthma. These results reinforce the positive association between grandmaternal smoking and childhood asthma under the age of 5 to 7 years described in three earlier studies.^{9,12,13} The study population included by Li *et al* is age comparable to the adult group in this study, although, the same cannot be said for the studied populations of Lodge *et al* and Magnus *et al*. However, the outcomes of these studies deviated from that of ours by focusing mainly on symptoms of asthma and/or use of asthma medication including sole usage of B agonist inhaler in childhood.

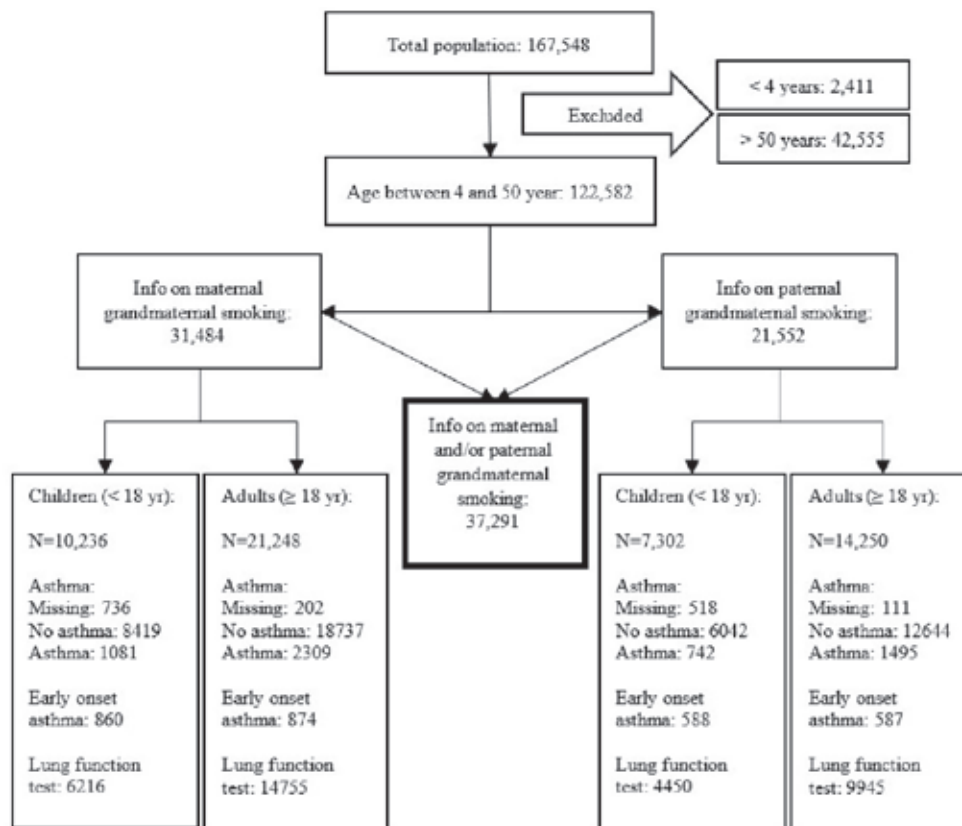


Figure 2 The selection of the population included in this study. First, participants were excluded based on age. Participants younger than 4 years of age or older than 50 years of age were excluded. Second, data spanning three generations was required to investigate a possible association between grandmaternal smoking during pregnancy and asthma in grandchildren. Therefore, participants who could not provide data on both childhood asthma and grandmaternal smoking were excluded. We investigated maternal grandmaternal smoking as well as paternal grandmaternal smoking and therefore those reporting on either one or both were included.

On the contrary, grandmaternal smoking during pregnancy exerted a protective effect in those grandchildren of younger generations (children group), born in the 1990s and onwards. This decreased risk for asthma and early childhood asthma, observed only in grandsons, is a new finding not previously reported in literature.

The contrasting results between the children and adult group in this study may be partly explained by the contrasting time periods associated with these groups, which allow for different trends in smoking habits and diagnosis of asthma. It can also be explained by the growing awareness of the adverse effects of smoking over the years and may have resulted in a healthy smoking family effect or in other words, lifestyle adaptations which contributed to an improved outcome for the generations that followed. This increasing awareness could also have caused selective reporting and recall bias of smoking during pregnancy.

Male grandchildren (F2) are more strongly affected by the effects of grandmaternal smoking compared with female grandchildren. The association between grandmaternal smoking during pregnancy and asthma in F2 males shown in this study's adult population has been reported in studies of nicotine exposure during pregnancy on airway hyperresponsiveness in rats.⁶ Human studies have demonstrated this same predilection for males of the F1 progeny exposed to maternal smoking.^{21,22} However, until now this has not been demonstrated in F2 progeny. Gender and sex hormones are thought to affect lung development, and this can be seen clinically due to the male predominance of asthma prevalence early in childhood. The gender specific effect in response to grandmaternal smoking during pregnancy may be related to this male predisposition for unfavourable lung development.²³ Conversely, the male specific protective effect of grandmaternal smoking during pregnancy seen in the children group of this study may relate to the study from Miller *et al*, where grandmaternal smoking, in the absence of maternal smoking, was associated with a more favourable birth weight in grandsons.²⁴

The secondary findings in our study differ from results of previous research. Unlike Li and colleagues, we showed that early childhood asthma risk associated with grandmaternal smoking is only significant in those with a non-smoking mother. Grandmaternal smoking during pregnancy does not only expose the fetus (F1), but also the gametes that will form the next (F2) generation. Therefore, our results suggest that if the mother smokes during pregnancy, the adverse effects on the fetus may have reached a maximum effect and are not stronger in those with additional grandmaternal exposure. Further to this, this study compared early childhood asthma and asthma at any age and from this can conclude that the higher risk for asthma is not only confined to the early childhood asthma phenotype but also applies to risk for asthma in older years.

Paternal smoking habits and exposure prior to conception has been shown to increase the risk for asthma in offspring.²⁵ Furthermore, paternal in utero smoke exposure (paternal grandmaternal smoking during pregnancy), has been linked with a higher risk for early childhood asthma specifically in granddaughters.¹⁰ However, in our study paternal grandmaternal smoking was not associated with asthma in grandchildren. Unfortunately, we were unable to investigate paternal smoking habits prior to conception and therefore, this interesting research question remains open for future study.

Grandmaternal smoking during pregnancy is associated with a lower lung function in grandchildren, specifically a lower FEV₁/FVC % predicted. This is exclusively seen in male grandchildren and parallels the higher risk for asthma in this group. The ALSPAC study is the only study to our knowledge to have previously addressed this association and reported no significant associations between grandmaternal smoking and lung function.¹⁰

The strengths of this study are that asthma outcomes were defined as doctor diagnosed or doctor treated asthma. This may have reduced the inclusion of non-asthmatic wheeze or bronchitis

Table 1 Descriptive statistics of subjects with information on gran-maternal smoking during pregnancy (maternal and/or paternal) stratified by age-group: children (>4 year and <18 year) and adults (≥18 year and ≤50 year)

	Children	Adults	P value
N	11 544	25 747	
Age, years	10.5 (3.7)	31.0 (8.4)	<0.001
Male gender	5638 (48.8)	9829 (38.2)	<0.001
Grandmaternal smoking			
Maternal	2501 (24.4)	1410 (6.6)	<0.001
Paternal	1374 (18.8)	686 (4.8)	<0.001
Maternal smoking	1226 (11.5)	4755 (20.8)	<0.001
Asthma	1214 (11.4)	2805 (11.0)	0.316
Early childhood asthma	967 (9.3)	1054 (4.4)	<0.001
Spirometry performed	7058 (61.1)	17 901 (69.5)	<0.001
FEV ₁ % predicted	95.2 (10.4)	95.2 (11.1)	0.732
FVC % predicted	96.3 (10.0)	98.6 (10.6)	<0.001
FEV ₁ /FVC	0.86 (0.06)	0.80 (0.07)	<0.001
FEV ₁ /FVC % predicted	98.2 (7.1)	96.0 (7.2)	<0.001
Active smoking			
Never	10 909 (95.7)	14 322 (58.7)	
Ex	98 (0.9)	4463 (18.3)	<0.001
Current	391 (3.4)	5616 (23.0)	
ETS in childhood			
No	7600 (71.0)	9831 (39.7)	
Yes	2045 (19.1)	14 785 (59.7)	<0.001
Unknown	1056 (9.9)	148 (0.6)	
Maternal age, years	29.8 (4.1)	26.9 (4.1)	<0.001
Birth weight, g	3499.1 (616.0)	3434.7 (580.9)	<0.001
Gestational age, years	39.6 (2.0)	39.8 (1.8)	<0.001
Breast feeding			
No	1967 (18.5)	6157 (25.0)	
Yes	8677 (81.4)	17 485 (71.0)	<0.001
Unknown	10 (0.1)	977 (4.0)	
Income			
<1000	167 (1.4)	4755 (18.5)	
1000–2000	1317 (11.4)	5297 (20.6)	
2000–3000	3763 (32.6)	6204 (24.1)	<0.001
>3000	5286 (45.8)	6708 (26.1)	
other	1004 (8.7)	2781 (10.8)	
Education			
Low	406 (3.5)	1613 (6.3)	
Intermediate	5579 (48.4)	14 359 (55.8)	<0.001
High	5499 (47.7)	9437 (36.7)	
Other/unknown	54 (0.5)	336 (1.3)	

ETS, environmental tobacco smoke.

Table 2 Maternal grandmaternal smoking during pregnancy and risk for asthma and early childhood asthma in grandchildren. Stratified by gender and maternal smoking during pregnancy. Adjusted for gender, maternal smoking, current or former smoking, passive environmental smoke exposure in childhood, maternal age, birth weight, gestational age, breast feeding and socioeconomic status

	Children (<18 years)				Adults (≥18 years)			
	Asthma		Early childhood asthma		Asthma		Early childhood asthma	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Total	1081 cases/8419 controls		860 cases/8419 controls		2309 cases/18 737 controls		874 cases/18 737 controls	
Unadjusted	0.92 (0.79 to 1.06)	0.233	0.95 (0.81 to 1.12)	0.569	1.29 (1.10 to 1.51)	0.002	1.55 (1.23 to 1.96)	<0.001
Adjusted	0.88 (0.76 to 1.03)	0.107	0.92 (0.78 to 1.09)	0.322	1.18 (1.00 to 1.39)	0.051	1.35 (1.06 to 1.71)	0.013
Females	478 cases/4381 controls		348 cases/4381 controls		1443 cases/11 623 controls		454 cases/11 623 controls	
Unadjusted	1.08 (0.87 to 1.34)	0.464	1.22 (0.95 to 1.55)	0.113	1.16 (0.94 to 1.42)	0.167	1.45 (1.05 to 2.01)	0.023
Adjusted	1.07 (0.86 to 1.34)	0.526	1.20 (0.94 to 1.54)	0.144	1.06 (0.86 to 1.31)	0.580	1.24 (0.89 to 1.73)	0.198
Males	603 cases/4038 controls		512 cases/4038 controls		866 cases/7114 controls		420 cases/7114 controls	
Unadjusted	0.79 (0.64 to 0.97)	0.026	0.79 (0.63 to 0.99)	0.043	1.54 (1.19 to 1.99)	0.001	1.73 (1.23 to 2.42)	0.001
Adjusted	0.74 (0.59 to 0.92)	0.006	0.74 (0.59 to 0.93)	0.011	1.38 (1.06 to 1.79)	0.016	1.49 (1.06 to 2.11)	0.023
Non-smoking mother	906 cases/7384 controls		742 cases/7384 controls		1608 cases/13 451 controls		616 cases/13 451 controls	
Unadjusted	0.88 (0.74 to 1.04)	0.143	0.96 (0.80 to 1.15)	0.657	1.21 (0.98 to 1.50)	0.077	1.51 (1.12 to 2.05)	0.007
Adjusted	0.86 (0.72 to 1.02)	0.088	0.93 (0.77 to 1.12)	0.439	1.14 (0.92 to 1.42)	0.228	1.32 (0.97 to 1.80)	0.076
Smoking mother	134 cases/950 controls		102 cases/950 controls		450 cases/3319 controls		160 cases/3319 controls	
Unadjusted	0.96 (0.66 to 1.39)	0.828	0.94 (0.62 to 1.43)	0.760	1.19 (0.88 to 1.61)	0.256	1.13 (0.69 to 1.85)	0.629
Adjusted	0.86 (0.58 to 1.26)	0.435	0.84 (0.54 to 1.31)	0.448	1.04 (0.77 to 1.42)	0.795	0.94 (0.57 to 1.56)	0.810

Percentages have been rounded and might not total 100.

*Age at the index date.

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

in childhood. First, the questionnaires included numerous questions about a participants' respiratory health. The asthma variable was constructed based on a response to a specific question about having asthma that was diagnosed by a doctor. Participants were asked separately about other respiratory conditions including wheezing, dyspnoea and bronchitis. The opportunity to report on various other respiratory illnesses alongside the specific reporting of asthma in these questionnaires should minimise misclassification. Second, we acknowledge that viral-induced wheeze may be confused for asthma in young children. In the attempt to exclude this group, the sole use of beta-agonist inhalers was not considered in defining asthma. While these approaches should minimise misclassification, we acknowledge that defining early onset asthma is difficult in an epidemiological setting.²⁶ Furthermore, a comparative investigation of the outcomes of both early childhood asthma and asthma was performed, lung function was investigated as an outcome represented by objective measurements, and this study adjusted for many confounders including environmental smoke exposure which is omitted in many previous studies. The limitations of this study include the retrospective means of data collection on smoking during pregnancy and age of asthma onset which may be subject to recall bias or selective reporting, which may lead to an overestimation of the associations. This recall bias and selective reporting is difficult to avoid and would require long-running, prospective studies to eliminate this. However, while we can expect some bias when reporting respiratory symptoms in grandchildren and maternal smoking we expect that this bias is less evident when reporting respiratory symptoms in grandchildren and grandmaternal smoking, as this association is less likely recognised between these generations. Due to the limited availability of three generation families with complete data on grandmaternal smoking, we were unable to include the full cohort in our analyses. We acknowledge that including those only with information on grandmaternal smoking in our analyses may result in bias. The included population consisted of a greater number of younger (<18 years) and non-smoking participants and had a lower prevalence of maternal smoking during pregnancy and environmental smoke exposure during childhood and a higher prevalence of asthma and being breast fed compared with the non-included population. The significant differences in lung function, income and education between the included and non-included groups were very small. The difference in age between groups was inherent to

Table 3 Maternal grandmaternal smoking during pregnancy and FEV₁/FVC % predicted. Stratified by gender and maternal smoking during pregnancy. Adjusted for gender, maternal smoking, current or former smoking, passive environmental smoke exposure in childhood, maternal age, birth weight, gestational age, breast feeding and socioeconomic status

	Children (<18 years)		Adults (≥18 years)	
	Beta-coefficient (95% CI)	P value	Beta-coefficient (95% CI)	P value
Total	n=6216		n=14 752	
Unadjusted	−0.32 (−0.75 to 0.1)	0.136	−0.3 (−0.79 to 0.2)	0.238
Adjusted	−0.15 (−0.57 to 0.28)	0.503	−0.19 (−0.68 to 0.30)	0.445
Females	n=3376		n=9163	
Unadjusted	−0.43 (−0.98 to 0.12)	0.123	0.20 (−0.39 to 0.79)	0.510
Adjusted	−0.23 (−0.78 to 0.32)	0.412	0.31 (−0.29 to 0.90)	0.311
Males	n=2840		n=5589	
Unadjusted	−0.18 (−0.84 to 0.49)	0.599	−1.15 (−2.02 to −0.28)	0.010
Adjusted	−0.06 (−0.73 to 0.60)	0.852	−1.04 (−1.91 to −0.16))	0.020
Non-smoking mother	n=5030		n=10 505	
Unadjusted	−0.29 (−0.78 to 0.20)	0.243	0.33 (−0.31 to 0.98)	0.308
Adjusted	−0.25 (−0.74 to 0.23)	0.308	0.25 (−0.39 to 0.89)	0.443
Smoking mother	n=710		n=2736	
Unadjusted	0.09 (−0.99 to 1.18)	0.867	−0.80 (−1.69 to 0.09)	0.077
Adjusted	0.03 (−1.07 to 1.13)	0.960	−0.91 (−1.81 to −0.01))	0.047

the study design as we did not have information on grandmaternal smoking in subjects older than 50 years of age. In this study, a dose-response relationship could not be established since the amount of grandmaternal smoking during pregnancy was not available. Grandpaternal smoking prior to pregnancy was also not reported, therefore, we were unable to study the increased asthma risk in grandchildren associated with grandpaternal smoking before age 15 years.¹¹ In addition, we could not investigate the effect of grandmaternal passive smoking during pregnancy as this data was not available. A final limitation is that we were unable to investigate third generation offspring (F3). The transgenerational effect of smoking has also been shown in F3 progeny animal studies.²⁷ This mechanism of transgenerational inheritance is another potential important implication of smoking due to epigenetic effects that are inheritable across generations. Four-generational human studies are needed to investigate this which could be further strengthened by incorporating epigenetic investigations of biological matter itself.

CONCLUSION

In this study, we have shown that maternal grandmaternal smoking during pregnancy exercises a detrimental role in pulmonary health in predominantly male grandchildren of less recent generations and conversely, a protective role in male grandchildren of more recent generations. This is represented by a higher asthma risk, paralleled by lower lung function and a lower asthma risk paralleled by favourable lung function, respectively. No association was found between paternal grandmaternal smoking during pregnancy and asthma in grandchildren.

It is important to realise that the results of this observational cross-sectional study may be subject to bias which can only be eliminated by means of future prospective studies. Our study contributes to the growing awareness of adverse intergenerational effects of smoking²⁸ and should stimulate further public health efforts to reduce smoking in the general population in particular before or during pregnancy.

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ORCID iDs

Gillian M Mahon <http://orcid.org/0000-0002-2659-1991>

Judith M Vonk <http://orcid.org/0000-0001-7531-4547>

REFERENCES

- Soriano JB, Abajobir AA, Abate KH, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the global burden of disease study 2015. *Lancet Respir Med* 2017;5:691–706.
- Joubert BR, Felix JF, Yousefi P, et al. DNA methylation in newborns and maternal smoking in pregnancy: genome-wide Consortium meta-analysis. *Am J Hum Genet* 2016;98:680–96.
- OECD iLibrary. Daily smokers. Available: https://www.oecd-ilibrary.org/social-issues-migration-health/daily-smokers/indicator/english_1ff488c2-en [Accessed 20 Dec 2019].
- Graham H. Smoking prevalence among women in the European community 1950–1990. *Soc Sci Med* 1996;43:243–54.
- Lanting CI, van Wouwe JPK, Burg Irvanden. [Smoking during pregnancy: trends between 2001 and 2010]. *Ned Tijdschr Geneesk* 2012;156:1–6.
- Rehan VK, Liu J, Naem E, et al. Perinatal nicotine exposure induces asthma in second generation offspring. *BMC Med* 2012;10:129.
- Singh SP, Chand HS, Langley RJ, et al. Gestational exposure to sidestream (Secondhand) cigarette smoke promotes transgenerational epigenetic transmission of exacerbated allergic asthma and bronchopulmonary dysplasia. *J Immunol* 2017;198:3815–22.
- Joubert BR, Häberg SE, Nilsen RM, et al. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. *Environ Health Perspect* 2012;120:1425–31.
- Li Y-F, Langholz B, Salam MT, et al. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. *Chest* 2005;127:1232–41.
- Miller LL, Henderson J, Northstone K, et al. Do grandmaternal smoking patterns influence the etiology of childhood asthma? *Chest* 2014;145:1213–8.
- Accordini S, Calciano L, Johannessen A, et al. A three-generation study on the association of tobacco smoking with asthma. *Int J Epidemiol* 2018;47:1106–17.
- Magnus MC, Häberg SE, Karlstad Øystein, et al. Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian mother and child cohort study. *Thorax* 2015;70:237–43.
- Lodge CJ, Bråbäck L, Lowe AJ, et al. Grandmaternal smoking increases asthma risk in grandchildren: a nationwide Swedish cohort. *Clin Exp Allergy* 2018;48:167–74.
- Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, et al. In utero exposure to cigarette smoking influences lung function at birth. *Eur Respir J* 1997;10:1774–9.
- Gilliland FD, Berhane K, McConnell R, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax* 2000;55:271–6.
- Zijlema WL, Smidt N, Klijns B, et al. The lifelines cohort study: a resource providing new opportunities for environmental epidemiology. *Arch Public Health* 2016;74:1–11.
- Scholten S, Smidt N, Swertz MA, et al. Cohort profile: lifelines, a three-generation cohort study and Biobank. *Int J Epidemiol* 2015;44:1172–80.
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-Ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
- van Zon SKR, Bültmann U, Mendes de Leon CF, et al. Absolute and relative socioeconomic health inequalities across age groups. *PLoS One* 2015;10:e0145947.
- IBM, Corp. IBM SPSS statistics for windows, 2013.
- Werteleeki W, Hoff C, Zansky S. Maternal smoking: greater effect on males, fetal tobacco syndrome? *Teratology* 1987;35:317–20.
- Zaren B, Lindmark G, Bakketeig L. Maternal smoking affects fetal growth more in the male fetus. *Paediatr Perinat Epidemiol* 2000;14:118–26.
- Carey MA, Card JW, Voltz JW, et al. It's all about sex: gender, lung development and lung disease. *Trends Endocrinol Metab* 2007;18:308–13.
- Miller LL, Pembrey M, Davey Smith G, et al. Is the growth of the fetus of a nonsmoking mother influenced by the smoking of either grandmother while pregnant? *PLoS One* 2014;9:e86781.
- Swane C, Koplun J, Skulstad SM, et al. Father's environment before conception and asthma risk in his children: a multi-generation analysis of the respiratory health in northern Europe study. *Int J Epidemiol* 2017;46:235–45.
- Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet* 2018;391:350–400.
- Rehan VK, Liu J, Sakurai R, et al. Perinatal nicotine-induced transgenerational asthma. *Am J Physiol Lung Cell Mol Physiol* 2013;305:L501–7.
- Melen E, Barouki R, Barry M, et al. Promoting respiratory public health through epigenetics research: an ERS environment health Committee workshop report. *Eur Respir J* 2018;51:1702410.

ARTIGO ORIGINAL INVESTIGAÇÃO

O efeito a longo prazo da tuberculose pulmonar sobre o rendimento e o emprego em contexto urbano de baixos rendimentos

Jamilah Meghji,^{1,2} Stefanie Gregorius,^{1,3} Jason Madan,⁴ Fatima Chitimbe,² Rachael Thomson,¹ Jamie Rylance,^{1,2} Ndazona PK Banda,⁵ Stephen B Gordon,^{1,2} Elizabeth L Corbett,⁶ Kevin Mortimer,¹ Stephen Bertel Squire¹

¹Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

²Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre, Malawi

³Deutsche Gesellschaft für Internationale Zusammenarbeit, Bonn, Germany

⁴Warwick Clinical Trials Unit, University of Warwick, Coventry, UK

⁵Department of Medicine, Queen Elizabeth Central Hospital, Blantyre, Malawi

⁶Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

Correspondence to

Dr Jamilah Meghji, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK; jamilah.meghji@lstm.ac.uk

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RESUMO

Contexto A atenuação do impacto sócio-económico da tuberculose (TB) é fundamental para a Estratégia de erradicação da TB da OMS. No entanto, pouco se conhece sobre o bem-estar sócio-económico depois da conclusão dos tratamentos para a tuberculose. Neste estudo de métodos mistos, descrevemos os resultados socioeconómicos pós-tuberculose na zona urbana de Blantyre, no Malawi, e exploramos caminhos e barreiras para a recuperação financeira.

Métodos Adultos ≥15 anos que completaram com sucesso o tratamento para um primeiro episódio de TB pulmonar ao abrigo do Programa Nacional de Controlo da TB foram seguidos prospectivamente durante 12 meses. Foram recolhidos dados socioeconómicos relativamente a rendimentos, profissão, procura por cuidados de saúde e despesa. Os determinantes e impactos das dificuldades financeiras correntes foram analisados através de entrevistas descritivas da doença com participantes propositadamente selecionados.

Resultados Foram recrutados 405 participantes entre fevereiro de 2016 e abril de 2017. A idade média foi de 35 anos (IQR: 28–41), 67,9% (275/405) eram do sexo masculino e 60,6% (244/405) estavam seropositivos. O emprego e os rendimentos eram mais baixos na conclusão do tratamento da tuberculose, com recuperação limitada no ano seguinte: menos pessoas tinham trabalho remunerado (63,0% (232/368) vs. 72,4% (293/405), $p=0,006$), os rendimentos medianos eram mais baixos (US\$44,13 (IQR: US\$0–US\$106,15) vs. US\$72,20 (IQR: US\$26,71–US\$173,29), $p<0,001$) e mais doentes viviam em situação de pobreza (auferindo <US\$1,90/dia: 57,7% (211/366) vs. 41,6% (166/399), $p<0,001$) 1 ano após a conclusão do tratamento da tuberculose, comparativamente ao período anterior ao início da doença. Metade dos participantes (50,5%, 184/368) reportaram uso das poupanças de forma contínua (recurso à poupança, venda de ativos, empréstimo de dinheiro) e 9,5% (35/368) reportaram interrupções escolares no ano após a conclusão do tratamento da tuberculose. Vinte e um participantes completaram entrevistas exaustivas. Entre os obstáculos reportados para a recuperação económica, contam-se a insegurança financeira, as dificuldades no restabelecimento de relações comerciais, a morbidez física residual e o estigma.

Conclusões As famílias afetadas pela tuberculose permanecem economicamente vulneráveis mesmo após a conclusão do tratamento, com uma recuperação limitada do rendimento e do emprego, tensão financeira persistente que requer uso das poupanças e interrupções escolares contínuas. As medições do impacto económico da doença da tuberculose deveriam incluir o período pós-TB. As intervenções para proteger a saúde a longo prazo e a subsistência dos sobreviventes da TB devem ser exploradas.

INTRODUCTION

An estimated 10million incident cases of tuberculosis (TB) disease occurred globally in 2018,

Key messages

What is the key question?

► What is the lasting socioeconomic impact of tuberculosis (TB) disease on patients and households: can we assume full economic recovery after successful treatment completion, and what are the pathways and barriers to this recovery?

What is the bottom line?

► Many TB-affected households experience a limited recovery in income and employment in the year after TB-treatment completion, with ongoing dissaving and school interruptions. Barriers to economic recovery include persistent financial insecurity, challenges rebuilding business relationships, residual physical morbidity and stigma.

Why read on?

► The socioeconomic impact of TB disease persists well beyond TB-treatment completion. Understanding this process, and developing strategies to mitigate this, will be crucial if we are to meet the WHO End TB Strategy target of eliminating TB-related catastrophic costs by 2030, and improve the long-term well-being of TB survivors.

onequarter of which occurred in Africa where 29% of patients are HIV coinfectd.¹ The early costs associated with TB disease in low-income settings are well recognised: despite provision of free TB-treatment services within the public sector, patients incur direct costs related to health seeking, indirect costs from lost income, and dissaving (the use of savings, borrowing of money, or sale of household assets) over the course of illness, diagnosis and treatment.^{2–3} These early costs are widespread, frequently profound and have been associated with adverse TB-treatment outcomes including treatment failure, loss to follow-up or death.⁴ However, surprisingly little is known about the lasting economic impact of disease beyond TB-treatment completion, and facilitators or barriers to economic recovery.

The physical effects of pulmonary-TB (PTB) are felt long after treatment completion: mortality rates are three to fourfold higher among TB survivors compared with TB-naïve adults,⁵ TB survivors have a high risk of disease recurrence,⁶ and the burden of residual post-TB lung disease (PTLD) is marked.^{7–8} Limited data are available on long-term psychosocial morbidities, but reports from TB-affected communities suggest

these are considerable.^{9,10} It is plausible that the ongoing physical and psychosocial impact of TB disease is accompanied by long-term economic harm. Understanding this link will be key to improving the overall well-being of TB survivors,^{11,12} and essential if we are to meet the WHO End TB Strategy target of eliminating catastrophic costs for all TB-affected households by 2030.¹³

Malawi is one of the poorest countries in the world,¹⁴ with an estimated national TB incidence of 181/100 000 in 2018.¹⁵ In this mixed-methods study, nested within a prospective cohort of adults successfully treated for PTB in urban Blantyre, Malawi,¹⁶ we describe economic morbidity in the year after TB-treatment completion, and explore its determinants and impacts.

METHODS

Full methods of the parent cohort study have been described previously.¹⁶ In brief, 405 sequential HIV-positive and HIV negative patients successfully completing treatment for PTB were recruited between February 2016 and April 2017 in urban Blantyre, Malawi. Inclusion criteria were age ≥ 15 years, and successful completion of treatment for a first episode of TB as defined by the National TB Control Programme (NTP). We excluded patients who had been treated for multidrug resistant disease. All participants provided written informed consent.

Study visits were conducted within 1 month of TB-treatment completion, and at 6 and 12 months thereafter. Questionnaires were completed in the local language, Chichewa. We collected data on demographics, socioeconomic situation (SES), TB and respiratory symptoms, quality of life, main occupation and income at each study visit. Patients provided information on occupation and income prior to TB illness from memory. Data on ongoing health seeking and associated direct and indirect costs were collected prospectively. Occupation was described using categories defined by the Malawi Demographic Health Survey 2015–2016.¹⁷ Income and dissaving questions were adapted from the STOP TB costing questionnaire.¹⁸ Monthly income was defined as money received by the individual, from work or other means, and was standardised into US dollars (online supplemental S1 appendix). Socioeconomic status was defined at TB-treatment completion using the Malawi EquityTool 2012.¹⁹ Information on TB microbiology at diagnosis was collected from NTP registers. HIV care is provided in a separate programme in this setting, and patient-held health passports were therefore reviewed to ascertain HIV status and antiretroviral therapy (ART) use, with HIV testing offered to all those with unknown serostatus who had not had a documented test within the past 1 month (Serial testing with Determine 1/2; Alere, USA/UniGold; Recombigen HIV, Trinity Biotech, Ireland). CD4 counts were measured in all HIV-positive participants.

Illness narrative interviews were conducted with purposively selected patients who had completed TB treatment ≥ 12 months previously, in order to explore their experiences of TB illness and recovery.²⁰ Recruitment ensured variation in gender, HIV status and socioeconomic status, and was stopped at the point of saturation. Interviews were conducted in Chichewa by a Malawian research assistant in a private location of the participant's choice, most frequently their home, using a pre-designed interview guide structured around the illness trajectory (life before, during and after TB treatment), which addressed issues of health, healthcare seeking behaviour and experiences, socioeconomic well-being, family and community life (online supplemental S2 appendix). Interviews were audiorecorded, transcribed into Chichewa, and translated into English. Notes and observations recorded by the study team were included as primary data.

All participants were compensated for their time and travel costs, in keeping with local ethics guidelines. The amount received

over the 1-year study period was the equivalent of US\$15.30 per participant.

Sample size

The sample size of 400 was predetermined by the parent study, in order to allow the prevalence of PTLD to be estimated with $\pm 5\%$ precision and 95% confidence.

Data analysis

Quantitative data were analysed using Stata V.15 (StataCorp). Health economic parameters are presented for each time point using median (IQR) values. χ^2 test, Fisher's exact or Wilcoxon rank-sum tests were used for comparisons between participant groups, and McNemar's test used for within-group comparisons over time. Individuals were classified by occupation into those with paid work (self-employed, formally employed (in government, non-governmental organisations, private sector), farming, domestic work, informal piece-work), unpaid work (housework, students) and no work (retired, unemployed). Participants were considered to be living in poverty if earning $< \text{US\$}1.90/\text{day}$.²¹

Logistic and linear regression models were used to explore the relationship between PTLD and economic outcomes, controlling for prespecified covariates recorded at TB-treatment completion (age, gender, HIV status, TB microbiology, educational level). Qualitative data were analysed thematically using an inductive framework approach²²; transcripts were discussed, a coding and thematic framework was developed iteratively, relationships between codes and themes were identified manually, and emerging links were cross-checked by discussion with the study team and triangulation with study team notes.

RESULTS

Patient population

A total of 450 PTB survivors were screened, and 405 met inclusion criteria (figure 1). The 37/405 (9.1%) participants who did not complete the final study visit had similar characteristics (age, sex, HIV status, TB microbiology, SES) to those who completed the study, but lower average CD4 counts at TB-treatment completion (113 cells/ μL (IQR: 62–197) vs 244 cells/ μL (IQR: 137–398), $p=0.007$) (online supplemental S3 appendix).

The majority of participants (67.9% (275/405)) were male, 77.3% (313/405) had microbiologically proven PTB disease, and 60.6% (244/403) were HIV-positive. Over half were from the lowest three urban wealth quintiles (54.3% (202/372)) and 38.0% (154/405) had not attended school beyond primary level. The 21 participants purposively selected for in-depth interviews had similar demographic and socioeconomic characteristics to other study participants, but a longer duration of illness prior to TB treatment (13.0 vs 8.7 weeks, $p<0.001$), and less formal education (38.1 (8/21) vs 63.3% (243/384) beyond primary school, $p=0.021$) (table 1).

Economic morbidity, after TB-treatment completion

Occupation and income

The proportion of participants in paid work fell during TB disease to a nadir of 54.8% (222/405) at TB-treatment completion, with 36.5% (148/405) unemployment (National unemployment rates 5.4%–5.7% between 2016 and 2018).²³ One year later, fewer participants were in paid work than prior to disease (63.0% (232/368) vs 72.4% (293/405), $p=0.003$), and the proportion of self-employed business people had not returned to previous levels (preillness: 32.8% (133/405); TB treatment end 26.9% (109/405); 1-year post-treatment completion 25.8% (95/368), $p=0.026$). Patterns were similar for HIV-positive and negative participants (figure 2).

A fifth of participants (20.7%, 74/358) moved from paid or unpaid work prior to TB disease, to no work by 1 year after TB-treatment completion. Half of these individuals lost work

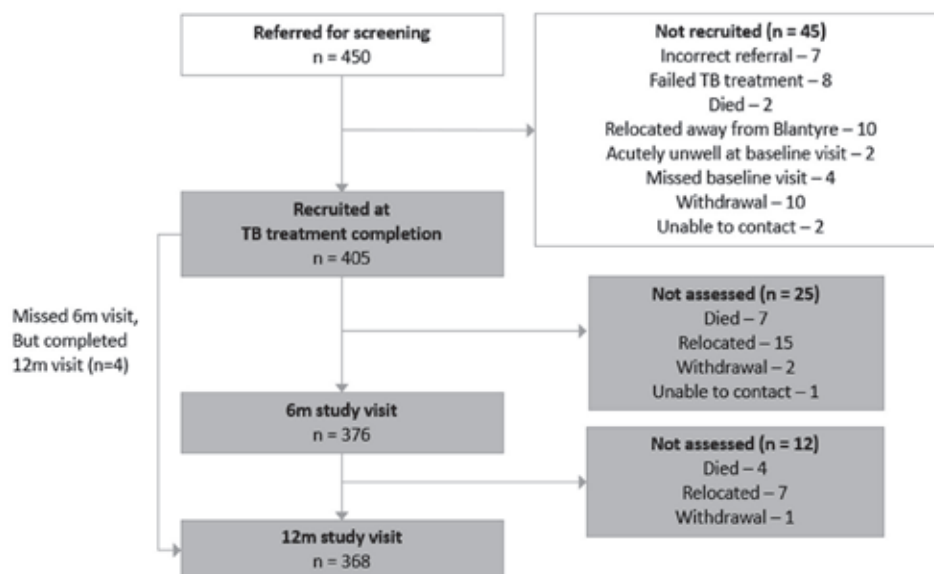


Figure 1 Participant flow diagram. TB, tuberculosis.

during TB disease and treatment (47.3%, 35/74), and half lost work in the year after treatment completion (52.7%, 39/74). Loss of work was more common in the lowest two versus highest three socioeconomic quintiles (28.6% (30/105) vs 15.9% (39/245), $p=0.004$). Among those who were employed prior to disease, 11.0% (17/154) had become self-employed by the end of follow-up.

Many participants did not know their total household income, including 40.7% (53/130) of women. However, individual incomes followed a similar pattern to that seen with work: median income was highest prior to TB illness, falling to a nadir at TB-treatment completion, with minimal recovery in the following year (figure 3). Monthly incomes fell by a median of \$11.59 (IQR for income difference: −72.20 to +12.89) from pre-illness to 1-year post treatment completion, with the greatest loss among those who were originally self-employed (−US\$74.96 (IQR: −231.99 to −7.01)). There was little difference in the median income loss experienced by the poorest two and wealthiest three socioeconomic quintiles over this period (−US\$11.78 (IQR: −56.73 to +16.63) vs −US\$10.77 (IQR: −77.23 to +11.60), $p=0.556$).

The proportion of participants living in poverty increased from 41.6% (166/399) to 57.7% (211/366) over this time ($p<0.001$), but the proportion of participants reporting that they were the highest earner in the household did not change (pre-

illness: 57.0% (231/405); TB-treatment end 54.6% (221/405); 1-year post treatment completion 60.6% (223/368)).

Healthcare costs

Direct healthcare costs in the year after TB-treatment completion were limited. Among those contributing any follow-up data, two-thirds of participants (66.8%, 254/380) had ≥ 1 outpatient visit, including 264 planned and 173 unscheduled visits, and 6.3% (24/380) had ≥ 1 inpatient admission. The majority of both outpatient visits (95.0%, 415/437) and admissions (88.9%, 24/27) occurred within the public sector. The majority of planned visits (87.1%, 230/264) were for appointments at ART clinics.

The median direct cost of an outpatient visit, including both planned and unscheduled visits, was US\$1.05 (IQR: 0.14–2.09), including expenditure for clinic fees and medications, and travel, accommodation, food and phone time for patients and guardians. The median time taken for any outpatient visit was 3 hours (IQR: 2–4), and loss of income was reported for 53.1% (232/437) of these visits, with average income time loss of 1 hour (IQR: 0–1) only. Guardians attended with study participants for a minority (8.2%, 36/437) of outpatient visits, and on these occasions rarely reported income time lost (5.6%, 2/36).

The median duration of the 27 inpatient admissions was four nights (IQR: 2–19), with median direct costs of US\$19.62

Table 1 Participant characteristics for participants included/ not included in nested qualitative work

Participant characteristic	Parent study only (n=384)	Parent and qualitative study (n=21)	p-value*
Age (years) (median, IQR)	34 (28–41)	35 (32–41)	0.246
Male sex (n, %)	261 (68.0%)	14 (66.7%)	0.901
Positive TB microbiology† at diagnosis (n, %)	299 (77.9%)	14 (66.7%)	0.233
Self-reported illness duration prior to TB treatment (weeks) (median, IQR)	8.7 (4.3–13.0)	13.0 (13.0–52.2)	<0.001
HIV-infected at TB-treatment completion (n=403)‡	232 (60.7)	12 (57.1)	0.743
ART use at TB-treatment completion (n, %) (n=244)	215 (92.7)	9 (75.0)	0.030
CD4 if HIV-positive at TB-treatment completion (cells/μL) (median, IQR) (n=242)	229 (127–397)	214 (126–420)	0.941
Maximum education level >primary school (n, %)	243 (63.3%)	8 (38.1%)	0.021
Urban SES quintile (n, %) (n=372) §			0.449
▶ Poorest	21 (6.0%)	1 (4.8%)	
▶ Second poorest	79 (22.5%)	6 (28.6%)	
▶ Middle	87 (24.8%)	8 (38.1%)	
▶ Second most wealthy	111 (31.6%)	3 (14.3%)	
▶ Most wealthy	53 (15.1%)	3 (14.3%)	

χ² test for categorical variables, Wilcoxon rank-sum test for continuous variables.

†Microbiology positive if smear, culture or Xpert MTB/RIF positive.

‡HIV status missing for two study participants.

§ Urban household wealth quintiles calculated from household characteristic and asset data, using a tool validated by the Malawi Malaria Indicator Survey 2012 (Equity measurement Toolkit; Social Franchising Metrics Working Group)¹⁹

ART, antiretroviral treatment; SES, socioeconomic situation; TB, tuberculosis.

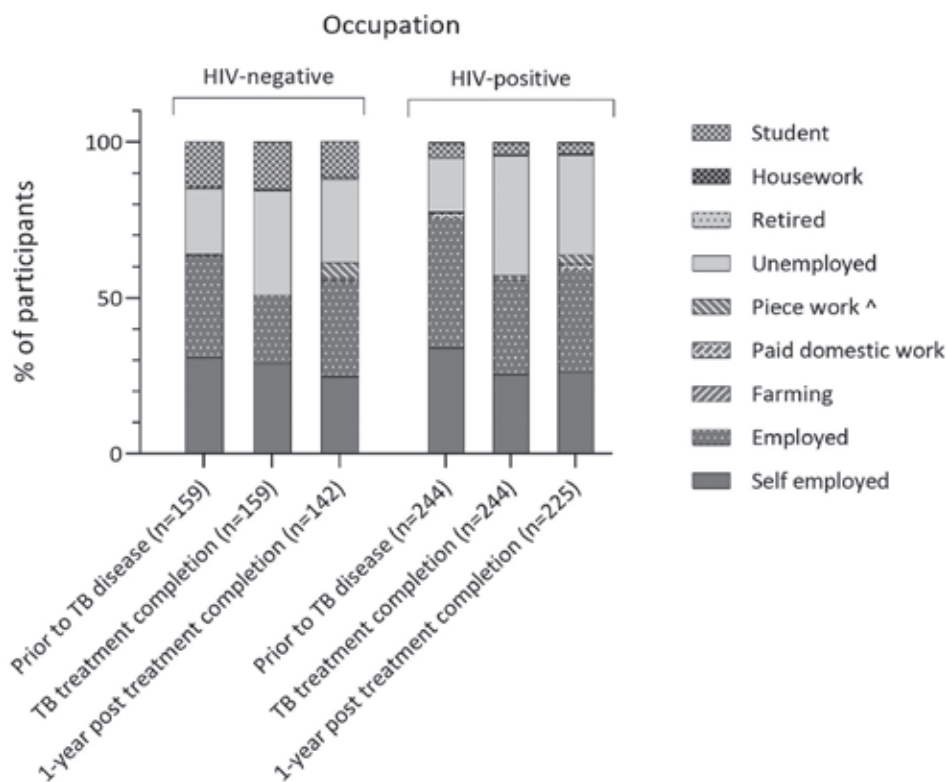


Figure 2 Self-reported occupation over time (prior to TB disease, at TB-treatment completion and 1-year after TB-treatment completion) stratified by HIV status. *HIV status available for 403 participants; *Ad hoc work (eg, washing clothes, driving of minibuses, carrying goods for others). TB, tuberculosis.

(IQR 13.30–61.91). Lost income was reported by participants for under a third of admissions (29.6%, 8/27), and although participants were accompanied by a guardian for the majority of these admissions (88.9%, 24/27) only one guardian reported lost income.

The proportion of participants attending ≥ 1 outpatient visit was similar in the lowest two, and top three socioeconomic quintiles (66.2% (73/107) vs 66.8% (177/265), $p=0.790$), and median per-visit costs were similar between socioeconomic groups (US\$0.84 vs US\$1.12, $p=0.578$). A higher proportion of participants from the lowest two socioeconomic quintiles required hospital admission compared with the top three quintiles (10.3% (11/107) vs 4.9% (13/265), $p=0.056$) but median per-admission costs were similar between groups (US\$19.27 vs US\$19.97, $p=0.750$).

Impact of economic morbidity, on patients and households

Interruption of a child's schooling due to the financial impact of illness was reported by 17.0% (69/405) and 9.5% (35/368) of TB-affected households in the years prior to and after TB-treatment completion, respectively. School interruptions were more common in the lowest two, compared with the top three, socioeconomic quintiles (32.1% (34/106) vs 17.7% (45/255), $p=0.003$).

Over a third of participants (37.0%, 150/405) reported that TB had had a severe financial impact on their household, graded $\geq 4/5$ on a Likert scale, at TB-treatment completion. This proportion was 16.9% (62/368) 1 year later. Self-reported severe financial impact was more common in the lower socioeconomic strata (58.5% (62/106) vs 37.4% (96/257), $p<0.001$).

Almost three-quarters of participants reported dissaving by the point of TB-treatment completion (73.6%, 298/405), and half reported dissaving in the following year (50.5%, 186/368), at values of 54.9% (IQR:24.3%–146.4%) and 53.2% (IQR:19.0%–125.7%) of the baseline monthly income prior to TB illness respectively. Over a quarter (26.7%, 27/101) of those with no dissaving during TB disease and treatment did go on to report dissaving in the year after treatment completion. Dissaving was more common in lower SES quintiles, but with lower absolute and relative values (table 2).

Patterns of dissaving varied by SES group, and over time (figure 4). All wealth strata used savings during the period of TB illness and treatment, but only the wealthiest quintiles used savings during the subsequent year. Borrowing money was the most common among lower socioeconomic strata, and over half of those in the lowest quintiles reported borrowing money in the year after TB-treatment completion. The most common sources of borrowed money were friends (44.8%, 172/384), family (26.8%, 103/384) and the black market (10.2%, 39/348)—use of the latter increased from 10.7% (19/177) in the first year to 17.1% (25/246) in the second year. The sale of assets to cover costs due to illness during the period of TB illness and treatment was also more common in poorer groups. The most common items sold were household items (35.0%, 134/383) and mobile phones (10.7%, 41/383). Potentially income-generating assets sold included land (1.3%, 5/383), livestock (3.7%, 14/383) and means of transport (4.7%, 18/383).

Relationship with TB retreatment

TB retreatment was initiated in 15/405 (3.7%) of participants, of whom five died, one relocated, and nine completed study follow-up. Socioeconomic outcomes were poor among those who survived and completed follow-up: by 1 year after TB-treatment completion, a higher proportion of those receiving retreatment had lost work (33.3% (3/9) vs 20.3% (71/349), $p=0.342$), experienced dissaving (100% (9/9) vs 79.4% (285/359), $p=0.128$), or reported a severe financial impact from TB disease (33.3% (3/9) vs 16.4% (59/359), $p=0.181$), compared with those who did not receive retreatment. However, none of these differences were statistically significant.

Relationship between physical and economic morbidity

Almost one-third of participants had abnormal spirometry (30.7%, 103/336) or regular respiratory symptoms (30.7%, 113/368) 1 year after TB-treatment completion. Those with abnormal spirometry were more likely to have lost work in the period from TB-illness onset, compared with those with normal spirometry (OR 1.87, 95%CI 1.02 to 3.41). Those with residual symptoms were more likely to report that TB had had a severe financial impact on the household, compared with those

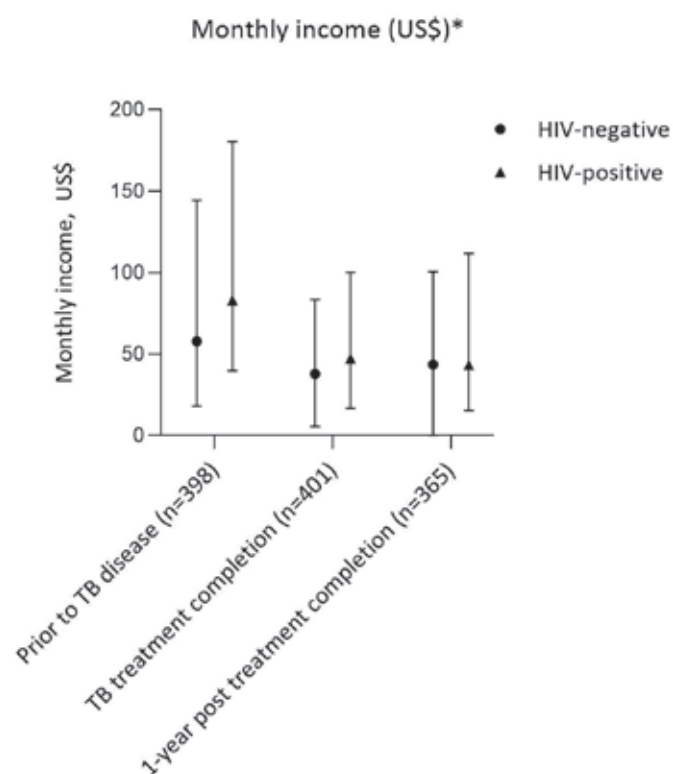


Figure 3 Self-reported income over time (prior to TB disease, at TB-treatment completion and 1-year after TB-treatment completion) stratified by HIV status (median, IQR)#. *Income data recorded in Malawian Kwacha with standardisation into US dollars by exchange rate at midpoint of pre-TB, baseline, and 1-year data collection intervals (online supplemental S1 appendix). #HIV status available for 403 participants. TB, tuberculosis.

without symptoms (2.02, 95%CI 1.10 to 3.68). Those with chest symptoms limiting their ability to keep up with peers (17.4%, 64/368), interfering with work (12.2%, 45/368) or limiting activities (4.4%, 16/368) at 1 year were significantly more likely to have experienced both of these outcomes. No significant association was observed between these measures of physical morbidity and the use of dissaving or change in income from pre illness to 1-year post TB-treatment completion (table 3).

Illness narratives

The persistent socioeconomic impact of TB disease was evident in the illness narrative data (table 4). The shift to a lower standard of living after TB disease was raised as a barrier to ongoing health and well-being. The need for further dissaving and withdrawal of children from school to release extra funds were highlighted as areas of concern.

Anxiety around loss of financial security, debt and the challenge of ongoing dependence on family and friends for support emerged as strong themes. A gendered response was seen with a perceived loss of social standing due to this dependence particularly common and problematic for men.

Reasons for limited recovery of income and work were explored. Ongoing physical morbidity was noted as a challenge to patients' livelihoods, however, participants largely continued to work despite residual symptoms in order to maintain income. Stigma was widely experienced and resulted in delayed return to work, or loss of work for those previously employed, with discrimination from colleagues often rooted in the perception that TB and HIV disease are linked. Loss of business infrastructure and the lack of capital to rebuild and reinvest was highlighted. Participants reported challenges in rebuilding business relationships which had been lost after a prolonged absence during the illness period, including those with employers, employees and customers.

DISCUSSION

In this study, we explore the long-term socioeconomic consequences of TB disease after TB-treatment completion. Our data show that the substantial financial insult experienced during TB illness extends to 12 months post-treatment completion. Economic recovery in the year after TB-treatment was slow and incomplete, with many patients continuing to experience income loss and reduced work. Persistent dissaving was widely observed and suggests increasing financial vulnerability. A substantial minority of patients experienced ongoing respiratory morbidity after treatment completion, and this was significantly associated with economic morbidity. Additional barriers to recovery after TB-treatment completion included ongoing financial insecurity from initial TB disease, reduced social capital and TB-related stigma.

Even in settings where TB services are free of charge within the public sector, the financial impact of TB disease is marked: a 2014 systematic review of 49 studies found that on average patients lost the equivalent of 58% (range 5%–306%) of annual individual income and 39% (range 4%–148%) of annual household income in direct and indirect costs during TB illness and treatment, with half of all costs incurred prior to treatment initiation.³ Those incurring 'catastrophic' costs ($\geq 20\%$ of annual household income) have been shown to have higher odds of adverse TB-treatment outcomes (death, treatment failure or recurrence).⁴

Our results support these findings of a major initial TB-related financial insult: during TB disease and treatment employment decreased, average patient incomes fell, and three-quarters of the cohort incurred dissaving. This pattern was seen across socioeconomic and employment groups, and by the end of TB-treatment the majority of TB survivors were living in poverty.

Table 2 Prevalence and value of dissaving in the years prior to and after TB-treatment completion, stratified by wealth quintiles*

	Malawi urban wealth quintile (Q1–Q5)†					
Participant characteristic	Q1 (n=56) Wealthiest	Q2 (n=114)	Q3 (n=95)	Q4 (n=85)	Q5 (n=22) Poorest	All participants
Prior to TB illness (n=372)						
Predisease monthly income (US\$)	108.30 (0–270.76)	83.03 (39.71–287.73)	63.18 (25.27–158.84)	61.37 (25.27–111.91)	41.52 (10.83–121.30)	72.20 (25.27–173.29)
During TB illness and treatment (n=372)						
Proportion incurring any dissaving	28/56 (50.0%)	83/114 (72.8%)	75/95 (79.0%)	68/85 (80.0%)	20/22 (90.9%)	274/372 (73.7%)
Value of dissaving, if experienced (US\$)‡	166.9 (94.58–423.50)	69.54 (34.77–173.85)	38.94 (15.30–115.44)	27.82 (16.69–80.95)	33.38 (13.91–100.39)	55.63 (20.86–139.08)
% of predisease monthly income (median, IQR)	89.2% (34.1–266.0)	58.2% (24.1–152.3)	53.9% (20.7–111.2)	41.6% (23.4–104.6)	44.1% (35.0–173.4)	54.9% (24.3–146.4)
Year after TB-treatment completion (n=360)						
Proportion incurring any dissaving	12/55 (21.8%)	48/107 (44.9%)	61/92 (66.3%)	50/84 (59.5%)	13/22 (59.1%)	184/360 (51.1%)
Value of dissaving, if experienced (US\$)‡	167.6 (59.36–272.35)	69.83 (24.1–152.3)	39.11 (20.95–92.18)	37.71 (13.97–69.83)	20.95 (11.17–31.42)	41.9 (20.95–94.97)
% of predisease monthly income (median, IQR)	112.5% (49.0–232.1)	77.6% (19.0–198.7)	59.3% (24.2–89.3)	41.9% (13.6–120.7)	29% (15.0–58.0)	53.2% (19.0–125.7)

*Values given for those who experienced dissaving, only.

†Baseline SES missing for 33 participants—data included for 372 participants only.

‡Standardisation into US\$ using exchange rates at midpoints of first and last study visits. SES, socioeconomic situation; TB, tuberculosis.

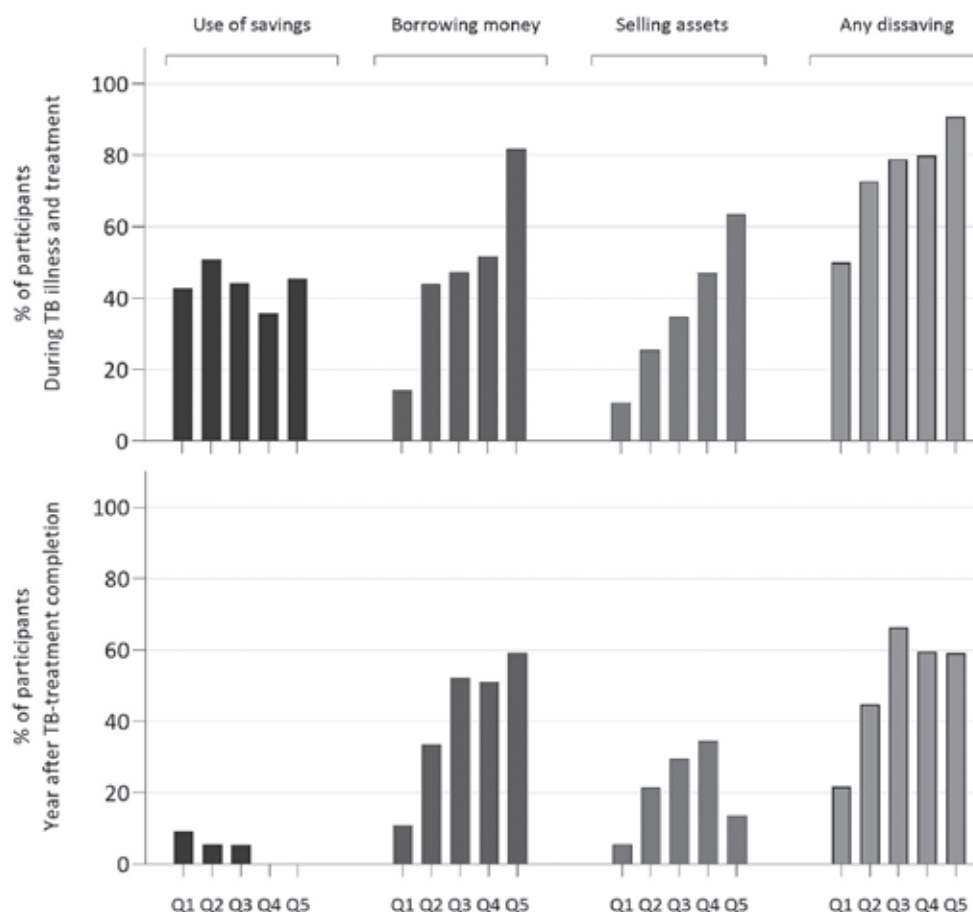


Figure 4 Proportion of participants incurring patterns of dissaving, during TB illness and treatment (n=372), and in the year after TB-treatment completion (n=360), stratified by urban wealth quintile (Q1–Q5)*.

Q1 – Q5: richest to poorest urban wealth quintiles, calculated at TB treatment completion using the Malawi Equity Tool 2012.

*Wealth quintile data missing for n=33 participants.

TB, tuberculosis.

However, our data also show that this impact is sustained, even after TB-treatment completion. Although the proportion of participants working increased in the year after TB-treatment completion, it did not return to baseline: 1 year after TB treatment, almost one-third of patients were unemployed, with standardised individual incomes lower than prior to illness. Self-employed individuals appeared particularly vulnerable, with large drops in income experienced by both those who were in work through their disease, as well as those who stopped working.

Post-TB physical morbidity was associated with limited recovery: abnormal spirometry, ongoing respiratory symptoms and chest symptoms limiting activity at 1 year were strongly associated with loss of work and perceived financial severity of the TB illness episode in multivariate analyses. Post-TB physical morbidity is increasingly recognised as a key component of the overall number of disability-adjusted and quality-adjusted life-years lost in relation to TB disease,²⁴ and our findings suggest that its impact on longterm productivity and financial vulnerability should also be considered.²⁵ Recurrent TB disease may also be detrimental to this group: socioeconomic outcomes among those receiving TB retreatment were poor in this study, but our ability to explore this finding was limited by the low numbers of retreatment patients identified, and further work is needed in this area.

In-depth interviews highlighted the loss of business assets during disease, with limited access to capital to rebuild after treatment completion as a major barrier to recovery. The challenge of rebuilding relationships with employers, employees and clients was emphasised, and attributed to a prolonged period of absence during TB illness and treatment, as well as loss of social standing due to impoverishment, disability, and the direct con-

sequences of TB-related and HIV-related stigma. The impact of TB-related stigma on patients' emotional well-being has been documented elsewhere,²⁶ but our data suggest that this also has socioeconomic repercussions.

Rather than promptly recovering, our data suggest that many TB survivors are at risk of further financial and psychological decline after TB-treatment completion. Dissaving is a coping mechanism for catastrophic costs,² and has been widely observed in TB-affected households during TB illness and treatment.²⁷ However, in this study, dissaving was observed in half of the cohort in the year after TB-treatment completion, including several households who had resisted dissaving during initial disease and treatment itself. Concern about dissaving was widely reported in the qualitative data. These findings suggest that even after TB-treatment completion, households continue to deplete their reserves or enter into further debt as they struggle to cover costs or seek to rebuild their lives and livelihoods.

Of particular concern, both the use of savings and the sale of assets declined in the post-treatment period, particularly among low socioeconomic strata, perhaps reflecting depletion of these resources. Instead, borrowing of money remained widespread with increasing use of the black market for loans, perhaps reflecting the exhaustion of more 'benign' sources of loans such as friends and family.

Interruption of children's education continued in 10% of households in the year after TB-treatment completion, and a high burden of anxiety related to financial insecurity, lower standard of living, and school interruptions was observed among TB survivors. Men voiced concern around loss of social standing, which is consistent with previous work describing high societal pressures on men to be effective providers, regardless of the difficulties of their circumstances.²⁸ Taken together, our quali-

Table 3 Adjusted ORs for associations between respiratory morbidity at 1-year post treatment completion, and economic outcomes over the study period, in multivariate analyses controlling for patient characteristics (age, gender, HIV status, TB microbiology, and educational level) at TB treatment completion

Physical morbidity	Loss of work (OR, 95%CI)			
	Loss of work (OR, 95%CI)	Use of dissaving (OR, 95%CI)	Income difference (β-coefficient, 95%CI)	Self reported severe financial impact of TB at 1year (OR, 95%CI)
Abnormal spirometry at 1 year	1.0	1.0	11.64 (−50.80 to 74.09)	1.0
▶ No	1.87 (1.02 to 3.41)	1.31 (0.71 to 2.43)		1.85 (0.96 to 3.58)
▶ Yes	p=0.042	p=0.393	p=0.714	p=0.066
Respiratory symptoms at 1 year	1.0	1.0	−6.34 (−63.01 to 50.33)	1.0
▶ No	1.26 (0.72 to 2.20)	0.79 (0.45 to 1.37)		2.02 (1.10 to 3.68)
▶ Yes	p=0.412	p=0.399	p=0.826	p=0.022
Difficulty keeping up with peers when walking at 1 year	1.0	1.0	7.26 (−62.80 to 77.31)	1.0
▶ No	2.39 (1.27 to 4.49)	0.61 (0.32 to 1.18)		2.04 (1.03 to 4.04)
▶ Yes	p=0.007	p=0.145	p=0.839	p=0.041
Chest symptoms interfering with/stopping work at 1 year	1.0	1.0	32.73 (−47.09 to 112.56)	1.0
▶ No	4.13 (2.06 to 8.28)	1.04 (0.45 to 2.39)		4.24 (2.08 to 8.66)
▶ Yes	p<0.001	p=0.934	p=0.421	p<0.001
Chest symptoms limiting most/all daily activities at 1 year	1.0	1.0	12.51 (−118/28 to 143.29)	1.0
▶ No	9.35 (3.02 to 28.95)	0.56 (0.17 to 1.85)		11.82 (3.74 to 37.33)
▶ Yes	p<0.001	p=0.340	p=0.851	p<0.001

Income difference: US\$ standardised change in monthly income from prior to TB disease, to 1-year post-TB-treatment completion.

Use of dissaving: any use of savings, borrowing of money or selling of assets from the onset of TB disease to 1-year post TB-treatment completion.

Loss of work: no longer working, having been in work (employed or self-employed) prior to TB disease.
TB, tuberculosis.

tative and quantitative data suggest that TB disease may push patients into an ongoing cycle of poverty, with many patients become increasingly financially vulnerable after TB-treatment completion, rather than experiencing financial recovery.

This study was performed at a single site and work from other resource-limited settings is needed to confirm findings. In the absence of a control group we cannot exclude the possibility that changes observed were related to general changes in the economy, although this is unlikely as unemployment within

Malawi was falling over the study period, changes in income persisted despite time-dependant standardisation into USD, and findings were consistent across qualitative and quantitative data.²³ Data on incomes and occupation prior to TB-illness onset, and healthcare costs between study visits were collected retrospectively, with some risk of recall bias. Our analyses used individual rather than household-level income data, perhaps leading us to underestimate participants' access to financial resources. The financial compensation provided for study par-

Table 4 Quotes from in-depth interviews with TB survivors

Theme	Quote
Impact of TB-related financial hardship on participants and households	
Reduced standard of living	'Since the time I was diagnosed with TB until now, I am staying in a bad looking house, with bad sleeping environment along with bad food' (female participant, 39 yrs) 'As [name of participant] hasn't been able to find work since he completed his treatment, the family had to move up the hill, where housing is cheaper. They also had to sell most of their furniture. There was only a mat on the floor, a little stool and a couple of mugs for a family of four... Another interesting observation we made relates to his relocation. Moving to cheaper accommodation on top of the hill means that he leaves the house less, as physical exercise remains a big challenge for him. This in turn limits his occupational activities and affects his health seeking behavior' (Research Assistant, relating to male participant, 32 yrs)
Anxiety around debt and financial insecurity	'I never used to have financial difficulties. Now, my business is just so small with borrowed capital and the creditors keep coming to my house, saying they want their money. If I fail to pay, there will be bigger interest. I have been in debts ever since I completed the treatment' (female participant, 29 yrs) 'Now, I am not having anything to eat and sometimes I don't have money to pay for rent. For example, I haven't paid rent yet. In the past, before I became sick, I could pay rent in advance' (male participant, 34 yrs) 'I have been facing financial challenges, lack of food and so on. In 2016, my girl failed to write her form two exams, due to lack of schooling that I couldn't pay for. So, I have faced so many difficulties from the time that I was diagnosed with TB until now' (female participant, 39 yrs) 'I used to sell our house equipment to sustain my family. So, we sold our TV and some small items. Others who could help us were living far from us and they can't just be helping you every day. Our children stopped going to school, so we had to sell whatever household equipment we had to sustain our living' (male participant, 32 yrs)
Dependence on others	'As of now, I have difficulties to get food, but I do try my level best to hunt for money to buy the food. My family supports me since I've completed treatment. Whenever I say that I don't have money to pay rental expenses and to buy food, they do send me the money' (female participant, 27 yrs)
Loss of social standing	'While I was sick and during the time when I completed my treatment people were not respecting me, but people were respecting me before I became unwell with TB. I think this is because I lost my income, and my family helps me. When you have money, people tend to respect you' (male participant, 34 yrs) 'He feels, once you have money, you have so much power and you can tell your employees what to do. In his case, his employees overtook power while he got sick, which still affects him' (Research Assistant, relating to a male participant, 34 yrs) When asked about how the income loss affects life: 'It has affected me a lot. I just feel depressed and sometimes I wonder if I am the same person'. (male participant, 18 yrs)
Barriers to income recovery	
Ongoing physical morbidity	'There are so many problems, I am facing these days because everything needs money... I still need to work, so I do some piece work, whether it means that I am still feeling pain, but I do work in order to get money to help myself.... The most important thing is to get money, so if you don't work then you have to do business in order to maintain your health and to fulfil your needs' (male participant, 37 yrs)
Stigma	'My boss said that I should wait at home during treatment... My boss accepted my TB diagnosis, but she didn't want me back after I completed' (female participant, 42 yrs) 'I went back to my work, but my boss discriminated against me and he told me that he wouldn't be helping me anymore financially, so I am just staying here at home' (male participant, 32 yrs) 'They [colleagues] would be surprised to see my work performance, which was dropping as I could sometimes work well one day and sometimes, I could not work well... they were saying that it was AIDS' (male participant, 18 yrs) 'The wife of the participant told us that she sells food items in front of the house and noted that some people don't want to buy from her, because they know that her husband is sick' (Research Assistant, relating to male participant, 32 yrs)
Loss of social and work relationships	'Our customers really had forgotten us, so I think it will take time for me to grow the business again' (male participant, 33 yrs)
Lack of capital for reinvestment	'My life has changed now... I have little capital... I don't do hard work now, so my employees help me do business. My business isn't the way it was before, because some of my business centers are closed now, I stopped selling Irish potatoes, I closed my take-away shops and I only have one bench of chips' (male participant, 48 yrs) 'The TB symptoms affected my business so much, to the extent that it went down up to date and it's not at all growing, though I was cured... My husband cannot even afford to give me MK 20,000.00 to start up a new business. I went to borrow money from someone on interest, but I haven't paid the person back. The capital you have determines what kind of business one engages in. So, instead of starting up a business with the little money borrowed, you start buying maize to feed children at home' (female participant, 39 yrs)

TB, tuberculosis.

ticipation may have acted as an additional source of income, cushioning participants from the of living, and school interruptions was observed among TB survivors. Men voiced concern around loss of social standing, which is consistent with previous work describing high societal pressures on men to be effective providers, regardless of the difficulties of their circumstances.²⁸ Taken together, our qualitative and quantitative data suggest that TB disease may push patients into an ongoing cycle of poverty, with many patients become increasingly financially vulnerable after TB-treatment completion, rather than experiencing financial recovery.

This study was performed at a single site and work from other resource-limited settings is needed to confirm findings. In the absence of a control group we cannot exclude the possibility that changes observed were related to general changes in the economy, although this is unlikely as unemployment within Malawi was falling over the study period, changes in income persisted despite time-dependant standardisation into USD, and findings were consistent across qualitative and quantitative data.²³ Data on incomes and occupation prior to TB-illness onset, and healthcare costs between study visits were collected retrospectively, with some risk of recall bias. Our analyses used individual rather than household-level income data, perhaps leading us to underestimate participants' access to financial resources. The financial compensation provided for study participation may have acted as an additional source of income, cushioning participants from the full financial hardship which may have been experienced under routine conditions.

Strengths of this study include its novel focus on patients' lives and livelihoods after TB-treatment completion, and use of mixed methods to understand participant perspectives and experiences. Qualitative data were collected to saturation, and the economic tools used were derived from validated sources. The study was conducted in an unselected population, with broad inclusion criteria, and minimal loss to follow-up, allowing broad generalisability.

Our findings have several key implications for TB research, policy and programmes. We recommend that studies investigating costs associated with TB disease should measure economic outcomes beyond TB-treatment completion. Recent data suggest that mortality rates among TB survivors are higher than that of TB-naïve individuals, and the extent to which the socioeconomic impact of TB disease contributes to this requires further investigation. Our findings suggest that interventions to protect livelihoods and prevent dissaving during disease may be crucial to the long-term well-being of TB-affected households. Microloans and training programmes to assist TB survivors to rebuild their livelihoods after treatment completion must be explored. These interventions should be codeveloped with TB-affected communities, and must be accompanied by community-level education programmes to address TB-related stigma. Ultimately, a renewed focus on physical, psychological and socioeconomic well-being after TB-treatment completion is needed if we are to improve the long-term outcomes of TB survivors.

Twitter Elizabeth L Corbett @LizCorbett17

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Contribution JMe, SBS, KM and SG were responsible for study conceptualisation and design. JMe led quantitative data collection and analysis, with senior guidance from JMa, KM and SBS. SG and FC performed qualitative data collection and analysis, with senior input from RT. JMe, JR and PB provided clinical oversight of the study cohort. SBS, KM, SBG and ELC provided senior input throughout the duration of the study. JMe was the lead author, with input from all coauthors. All authors read and approved the final manuscript for publication.

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ORCID iDs

Jamilah Meghji <http://orcid.org/0000-0002-4693-8884>

Jason Madan <http://orcid.org/0000-0003-4316-1480>

Rachael Thomson <http://orcid.org/0000-0001-5010-3428>

Jamie Rylance <http://orcid.org/0000-0002-2323-3611>

Stephen B Gordon <http://orcid.org/0000-0001-6576-1116>

Elizabeth L Corbett <http://orcid.org/0000-0002-3552-3181>

Kevin Mortimer <http://orcid.org/0000-0002-8118-8871>

Stephen Bertel Squire <http://orcid.org/0000-0001-7173-9038>

REFERENCES

- World Health Organisation. Global Tuberculosis Report, 2019. Geneva, Switzerland; 2019. 2019.
- Madan J, Lönnroth K, Laokri S, et al. What can dissaving tell us about catastrophic costs? linear and logistic regression analysis of the relationship between patient costs and financial coping strategies adopted by tuberculosis patients in Bangladesh, Tanzania and Bangalore, India. *BMC Health Serv Res* 2015;15:476.
- Tanimura T, Jaramillo E, Weil D, et al. Financial burden for tuberculosis patients in low and middle-income countries: a systematic review. *Eur Respir J* 2014;43:1763–75.
- Wingfield T, Boccia D, Tovar M, et al. Defining catastrophic costs and comparing their importance for adverse tuberculosis outcome with multi-drug resistance: a prospective cohort study, Peru. *PLoS Med* 2014;11:e1001675.
- Romanowski K, Baumann B, Basham CA, et al. Long-term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2019;19:1129–37.
- Marx FM, Floyd S, Ayles H, et al. High burden of prevalent tuberculosis among previously treated people in Southern Africa suggests potential for targeted control interventions. *Eur Respir J* 2016;48:1227–30.
- Amaral AF, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J* 2015;46:1104–12.
- Meghji J, Simpson H, Squire SB, et al. A systematic review of the prevalence and pattern of imaging defined post-TB lung disease. *PLoS One* 2016;11:e0161176.
- Harries AD, Dlodlo RA, Bridgen G, et al. Should we consider a 'fourth 90' for tuberculosis? *Int J Tuberc Lung Dis* 2019;19:1170–1.
- Allwood B, van der Zalm M, Makanda G, et al. The long shadow post-tuberculosis. *Lancet Infect Dis* 2019;19:1170–1.
- Datta S, Evans CA. Healthy survival after tuberculosis. *Lancet Infect Dis* 2019;19:1045–7.
- The Post-TB Symposium Steering Committee. 1st International Post-TB Symposium Proceedings. Stellenbosch, SA; 2019. Available: <https://www.post-tb-symposium.com> [Accessed 25th February 2020].
- World Health Organisation. The End TB Strategy. Geneva, Switzerland; 2015.
- The World Bank. Malawi Overview 2018. Available: <http://www.worldbank.org/en/country/malawi/overview> [Accessed 5th August 2020].
- World Health Organisation. TB Country Report, Malawi 2018. Geneva, Switzerland; 2018.
- Meghji J, Lesosky M, Joekes E, et al. Patient outcomes associated with posttuberculosis lung damage in Malawi: a prospective cohort study. *Thorax* 2020;75:269–78.
- Malawi National Statistics Office (NSO). Malawi Demographic & Health Survey, 2015–16. Zomba, Malawi and Rockville, Maryland, USA; 2017.
- Stop TB Partnership. Tool to estimate patient's costs. KNCV Tuberculosis Foundation, the World Health Organization and the Japan Anti-Tuberculosis Association; 2018.
- Social Franchising Metrics Working Group. Equity measurement toolkit: Malawi. Available: <https://www.equitytool.org/malawi/> [Accessed June 2015].
- Groleau D, Young A, Kirmayer LJ. The McGill Illness Narrative Interview (MINI): an interview schedule to elicit meanings and modes of reasoning related to illness experience. *Transcult Psychiatry* 2006;43:671–91.
- The World Bank. Measuring Poverty 2019. Available: <https://www.worldbank.org/en/topic/measuringpoverty> [Accessed 25th February 2020].
- Ritchie J, Spencer L, O'Connor W. Carrying Out Qualitative Analysis. In: Ritchie J, Lewis J, eds. *Qualitative research practice: a guide for social science students and researchers*. London, 2003.
- Statista. Malawi: Unemployment rate from 1998 to 2018. Available: <https://www.statista.com/statistics/808778/unemployment-rate-in-malawi/2018> [Accessed 20th January 2020].
- Miller TL, McNabb SJ, Hilsenrath P, et al. Personal and societal health quality lost to tuberculosis. *PLoS One* 2009;4:e5080.
- Quaife M, Houben R, Allwood B, et al. Post-tuberculosis mortality and morbidity: valuing the hidden epidemic. *Lancet Respir Med* 2020;8:332–3.
- Dias AA, de Oliveira DM, Turato ER, et al. Life experiences of patients who have completed tuberculosis treatment: a qualitative investigation in Southeast Brazil. *BMC Public Health* 2013;13:595.
- Ukwaja KN, Modebe O, Igwenyi C, et al. The economic burden of tuberculosis care for patients and households in Africa: a systematic review. *Int J Tuberc Lung Dis* 2012;16:733–9.
- Chikovre J, Hart G, Kumwenda M, et al. 'For a mere cough, men must just chew Conjex, gain strength, and continue working': the provider construction and tuberculosis care-seeking implications in Blantyre, Malawi. *Glob Health Action* 2015;8:26292.

Iniciativas para reduzir as terapêuticas na bronquiolite em serviço de urgência e cuidados de saúde primários

Marta Montejo,¹ Natalia Paniagua,² Carlos Saiz-Hernando,³ Lorea Martinez-Indart,⁴ Santiago Mintegi,^{2,5} Javier Benito^{2,5}

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¹Rontegi-Barakaldo Primary Care Center, University of the Basque Country, Bilbao, Spain

²Pediatric Emergency Department, Cruces University Hospital, Bilbao, Spain

³Department of Medical Documentation, Cruces University Hospital, Bilbao, Spain

⁴Epidemiology Department, Cruces University Hospital, Bilbao, Spain

⁵Department of Pediatrics, University of the Basque Country, Bilbao, Spain

Correspondence to

Dr Marta Montejo, RontegiBarakaldo Primary Care Center, University of the Basque Country, Bilbao 48940, Spain; Marta.montejofernandez@osakidetza.eus

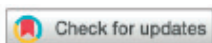
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RESUMO

Realizámos uma iniciativa de melhoria da qualidade para reduzir terapêuticas desnecessárias na bronquiolite aguda (BA) em cuidados de saúde primários (CSP) e em serviço de urgência pediátrica (UP) de referência. A iniciativa de melhoria da qualidade envolveu duas temporadas: 2016-2017 (pré-intervenção) e 2017-2018 (pós-intervenção). Distribuímos um protocolo com base em evidências, pôsteres informativos e crachás com o slogan “Bronchiolitis, less is more” (Bronquiolite, menos é mais). Também realizámos sessões interativas e os pediatras receberam relatórios semanais sobre prescrição de broncodilatadores. O principal resultado foi a percentagem de crianças a quem foi prescrito salbutamol.

Os resultados secundários foram taxas de prescrição de epinefrina, antibióticos e corticosteroides. As medidas de controlo foram as taxas de visita à UP e hospitalização, nível de triagem, duração da estadia, admissão em cuidados intensivos e regressos não previstos com internamento. Incluímos 1878 visitas à UP e 1192 visitas aos CSP, das quais 855 (44,5%) e 534 (44,7%) ocorreram no período pós-intervenção, respetivamente. Na UP, as taxas de prescrição de salbutamol e epinefrina caíram de 13,8% (95% IC 11,8% a 16%) para 9,1% (95% IC 7,3% a 11,2%) ($p<0,01$) e de 10,4% (95% IC 8,6% a 12,4%) para 9% (95% IC 7,2% a 11,1%) (n.s.), respetivamente. Nos CSP, as taxas de prescrição de salbutamol, corticosteroides e antibióticos caíram de 38,3% (IC 95% 34,6% a 42,0%) para 15,9% (IC 95% 12,9% a 19,5%) ($p<0,01$), de 12,9% (95% IC 10,5% a 15,7%) para 3,6% (95% IC 2,2% a 5,7%) ($p<0,01$) e de 29,6% (95% IC 26,2% a 33,2%) para 9,5% (95% IC 7,2% a 12,5%) ($p<0,01$), respetivamente. Não foram observadas variações significativas nas medidas de controlo. Diminuímos com segurança a utilização de tratamentos desnecessários para BA. A colaboração entre os CSP e a UP afigura-se como um fator importante para o sucesso.

INTRODUCTION

Acute bronchiolitis (AB) is the most common reason worldwide for non-elective hospital admission in infants <1 year of age.¹ Although evidence-based guidelines recommend primarily supportive care,^{2,3} many unnecessary treatments remain well documented, contributing to a care quality problem of overtreatment.^{4,5} In addition, despite the high incidence, increasing morbidity and significant economic impact of AB, there is still great variability in clinical practice, both in the diagnosis and management of this illness.^{6–8}

The implementation of evidence-based clinical practice guidelines (CPGs) has been reported to result in reductions in diagnostic and therapeutic resource use and improvements in clinical outcomes.^{9,10} Nevertheless, CPG implementation is complex, and there is still a gap between the evidence available and clinical practice.^{11–13} Specifically, despite a lack of supporting evidence, there continues to be a substantial amount of unnecessary testing and treatments with potential side effects and higher costs.^{13,14}

Quality improvement (QI) initiatives implemented in response to overtreatment problems

What is already known on this topic?

- Although evidence-based guidelines for acute bronchiolitis recommend primarily supportive care, many unnecessary treatments remain well documented, contributing to a care quality problem of overtreatment.

What this study adds?

- As our baseline use is probably comparable with current practice in other emergency department and primary care settings, our findings have implications for similar health areas wanting to undertake projects to improve the management of acute bronchiolitis.

have been shown to decrease the use of non-evidence-based therapies and testing and also provide achievable benchmarks of care for clinical quality indicators, especially in hospital settings.^{14–17} Nonetheless, less evidence is available from other settings, such as primary care (PC), where standardising treatment also requires a multifaceted approach, which is still a challenge.¹⁷

The objective was to implement and assess a QI initiative to reduce the overuse of unnecessary treatments in infants with AB in PC settings and the referral paediatric emergency department (ED).

PATIENTS AND METHODS

Setting

We conducted a QI initiative, evaluating the use of pharmacotherapies in children diagnosed with bronchiolitis, in two health districts and the referral paediatric ED.

Our healthcare system provides comprehensive, free and universal coverage. The two health districts involve 20 PC centres with 39 paediatricians who care for 36412 children, of whom 6371 (17.5%) are infants under 2 years old. The region where the study was carried out has two other health districts with 30 PC centres in which no interventions were performed.

The referral paediatric ED is located in an acute care teaching tertiary hospital near Bilbao, in the Basque Country (Spain). This department provides care to children under 14 years old, with a mean of 60000 emergency visits a year. Around 2% of these visits are due to AB. There is an observation unit in the ED, which is a 24-hour unit with 10 beds, staffed by paediatric emergency physicians.

We executed this QI initiative over two AB seasons: October–March of 2016–2017 (preintervention period) and October–March of 2017–2018 (postintervention period). All children under 2 years old

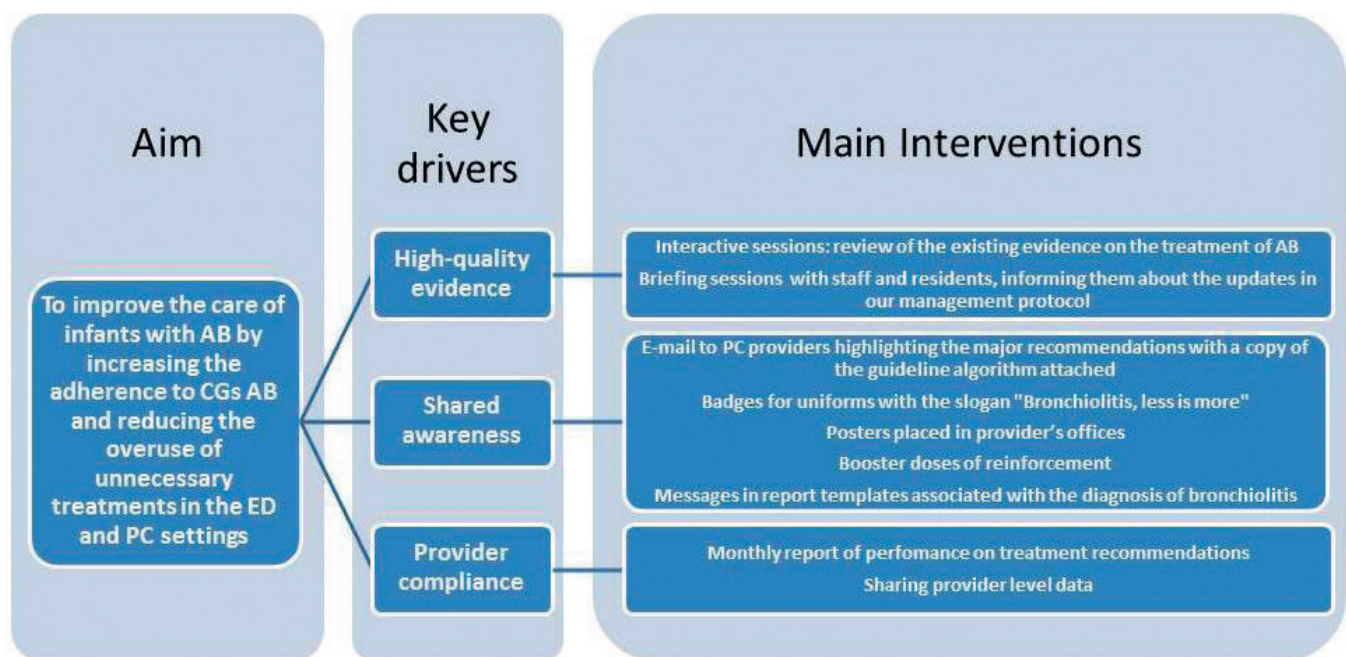


Figure 1 Key driver diagram. This tool displays the primary drivers (centre) or system factors affecting the project outcome listed in the aim (left). The interventions that were employed to address each primary driver are shown (right). AB, acute bronchiolitis; ED, emergency department; PC, primary care; CGs, clinical guidelines.

with a diagnosis of bronchiolitis, defined as the first presentation with a viral respiratory tract infection with respiratory distress,³ were included, regardless of whether they had comorbidities (lung or congenital heart disease, immunodeficiency, neuromuscular, neurological or genetic disease). Exclusion criteria were a previous diagnosis of bronchiolitis ≥ 1 month before the index episode.

Interventions

We assembled a multidisciplinary team, which consisted of paediatric PC physicians, paediatric emergency physicians, paediatric residents, paediatric nurses, nurses' aides and a clinical epidemiologist. A kickoff meeting was held to review data from previous bronchiolitis seasons and develop interventions (figure 1). A multifaceted plan was conducted in order to increase compliance with the CPGs and reduce unnecessary treatments in PC and the referral ED:

Educational campaign

Several briefings sessions were held, with staff and residents, informing them about the updates in our management protocol. In addition, we developed monthly interactive sessions with online data collection and feedback. The interactive sessions mainly consisted of reviewing the existing evidence on the treatment of AB and discussing barriers to applying what is known about this disease.

Informative tools

During epidemic months, informative posters for staff and families were placed in the common work area and also in the waiting room. Badges for uniforms with the project slogan 'Bronchiolitis, less is more' were distributed to staff.

Feedback on updated clinical quality indicators to paediatricians

Paediatricians received a weekly report with personal and global data on the prescription of bronchodilators in PC settings and the ED. In addition, they received monthly emails comparing their individual bronchodilator use rates to those of their unidentified peers.

Furthermore, global clinical quality indicators related to AB, such as rates of admission and unscheduled visits to the ED, were periodically updated and circulated via email to all paediatricians.

Update alerts in electronic health records

The option for a trial of bronchodilators was removed from the report templates associated with the diagnosis of bronchiolitis in the ED. Instead, reminder messages for clinicians were included about the recommendation on restricting the prescription of salbutamol.

Information for families

At the time of discharge, families were given an updated fact sheet with information on bronchiolitis including techniques of nasal washing and suctioning and how to recognise signs of distress.

Data collection system

A computerised search tool was used to identify patients with International Classification of Diseases-9 or 10 codes related to bronchiolitis for the respective time periods of data collection. Demographic, clinical and medical prescription data were collected from the computerised database system of the Basque Health Service. Informed consent from parents was not considered necessary because the children did not undergo any interventions related to this study, and data were handled anonymously.

Outcome measures

The primary outcome measure was the rate of infants with AB receiving salbutamol in the ED and the rate of prescription of salbutamol in PC settings.

Secondary outcomes evaluated were the rate of infants with AB receiving epinephrine, antibiotics and corticosteroids and the use of X-ray in the ED and the rate of prescription of antibiotics and corticosteroids in PC settings.

To evaluate the possible unintended consequences of decreasing interventions, we studied several balance outcome measures, defined as followed:

- Balance measure 1: overall rate of hospital admission.
- Balance measure 2: rate of paediatric intensive care unit (PICU) admission.
- Balance measure 3: length of stay in the ED.
- Balance measure 4: rate of unscheduled returns within 72 hours.
- Balance measure 5: rate of unscheduled returns with admission within 72 hours.

In addition, we obtain the rate of salbutamol prescription in PC settings during the two AB seasons for health areas in which no QI initiatives were performed.

Statistical analysis

Quantitative data were expressed as means and SD or medians and IQRs, depending on the distribution of the variables, and categorical variables using frequencies and percentages. Shewhart P charts¹⁸ were used to continuously evaluate outcome measures during the intervention phase. On each P chart, we plotted the outcome of interest on the vertical axis versus time on the horizontal axis. Each data point represents 7 days of data, and data from outside of bron-

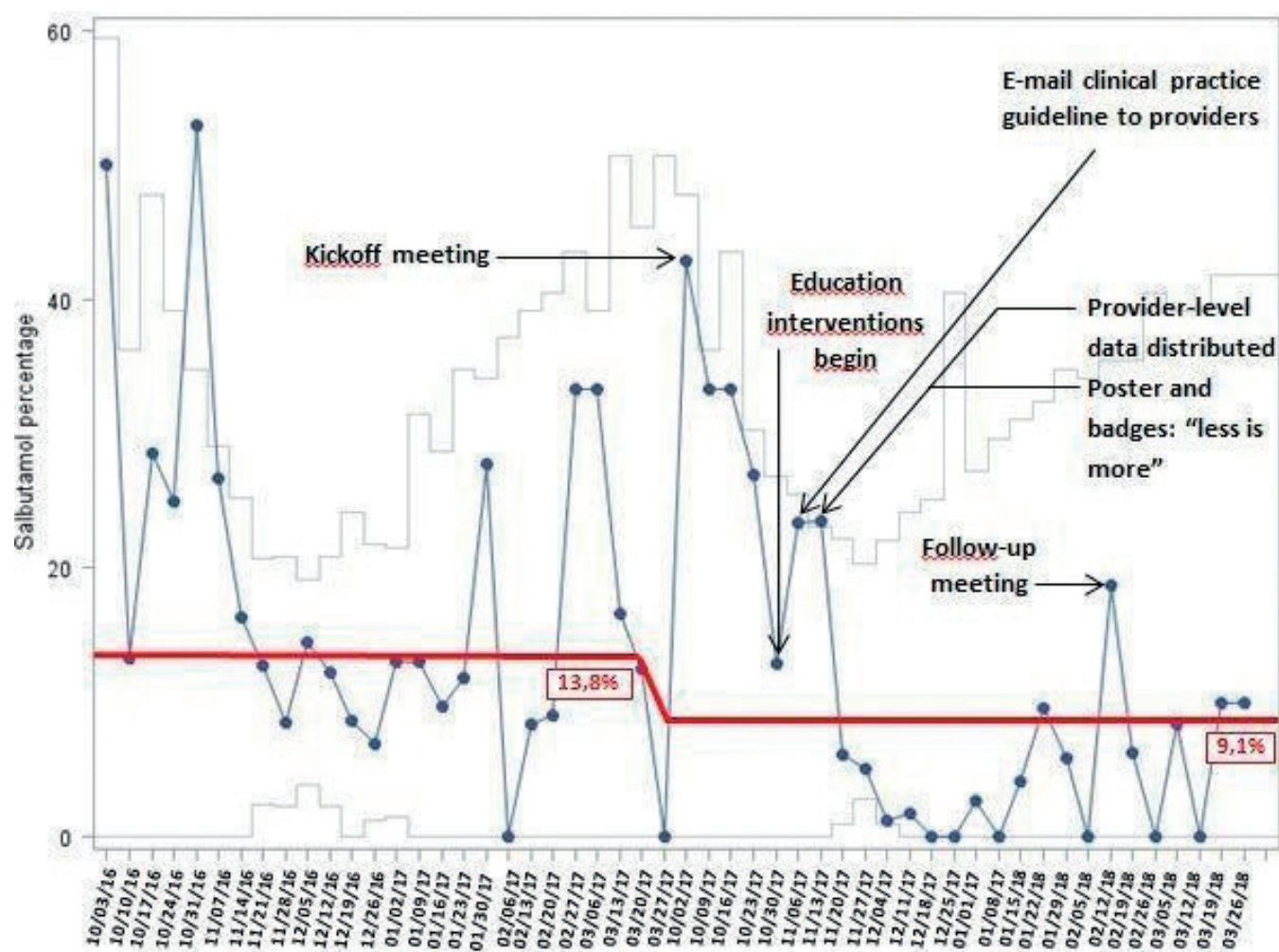


Figure 2 P chart showing decrease in the percentage of infants receiving salbutamol in the emergency department after implementation of the QI initiative. QI, quality improvement.

chilolitis season were not included in the analysis. The control limits were based on the binomial distribution of proportions, as indicated when an outcome is not rare. The timing of each intervention is indicated on the charts.

Associations between qualitative variables were assessed using the χ^2 test. Comparisons between variables with a normal distribution were made using the Student's t-test. The level of statistical significance chosen was $p < 0.05$. We carried out the statistical analysis using IBM SPSS Statistics for Windows (V.23).

RESULTS

Population characteristics

During the study period, 1878 episodes of AB were recorded in the ED (1023 in the preintervention period and 855 in the postintervention period) and 1192 in PC centres participating in the initiative (658 and 534, respectively). Among the episodes seen in the ED, 392 (38.3%) in the preintervention season and 333 (38.9%) in the postintervention season came from the PC centres in which the interventions were performed.

Overall, 1636 (87.1%) episodes seen in the ED and 888 (74.5%) episodes seen in PC settings were under 12 months of age, without significant differences between the two AB seasons.

Outcome measures

In the ED, there was a fall in the percentage of infants receiving salbutamol from 13.8% (95% CI 11.8% to 16%) to 9.1% (95% CI 7.3% to 11.2%; $p = 0.01$) (figure 2) and epinephrine from 10.4% (95% CI 8.6% to 12.4%) to 9% (95% CI 7.2% to 11.1%; not significant). The use of antibiotics did not vary significantly (2.4%; 95% CI 1.6% to 3.5% vs 3.1%; 95% CI 2.1% to 4.5%). The use of corticosteroids was less than 1% in the ED. The rate of X-ray did not vary significantly (7.7%; 95% CI 6.2% to 9.5% vs 7.8%; 95% CI 6.2% to 9.8%).

In PC settings, the rates of prescription of salbutamol, corticosteroids and antibiotics fell from 38.3% (95% CI 34.6 to 42.0%) to 15.9% (95% CI 12.9% to 19.5%) ($p < 0.01$) figure 3, from 12.9% (95% CI 10.5% to 15.7%) to 3.6% (95% CI 2.2% to 5.7%) ($p < 0.01$) and from 29.6% (95% CI 26.2% to 33.2%) to 9.5% (95% CI 7.2% to 12.5%) ($p < 0.01$) (table 1), respectively. The decrease in the use of salbutamol occurred in the 20 PC settings where the intervention was performed with great variability in the prescription rates (online supplementary figure).

Prescription rates of salbutamol in the preintervention and postintervention periods depending on age and acuity level at ED triage are shown in an online supplementary table.

A total of 1348 and 1225 episodes were diagnosed with AB in the PC centres from the two health districts without intervention in the 2016–2017 and 2017–2018 seasons, respectively. The overall salbutamol rate in these PC settings in the 2017–2018 AB season was significantly higher than those observed in PC settings from the health areas participating in the interventions (32.4%; 95% CI 29.9% to 35.1% and 15.9%; 95% CI 13.0% to 19.2%, respectively; $p < 0.01$). The overall prescription rate of salbutamol in these two areas in the preintervention AB season was similar than those observed in the intervened areas (33.6%; 95% CI 31.1 to 36.1% and 38.3%; 95% CI 34.6 to 42.0, respectively; $p = 0.04$).

Balancing measures

In brief, there was no change in the overall rates of hospitalisation, PICU admission, revisits or readmissions and length of stay in the ED after the interventions (table 2).

A total of 553 and 622 episodes were diagnosed with asthma in the ED in children under 2 years old in the 2016–2017 and 2017–2018 AB seasons, respectively.

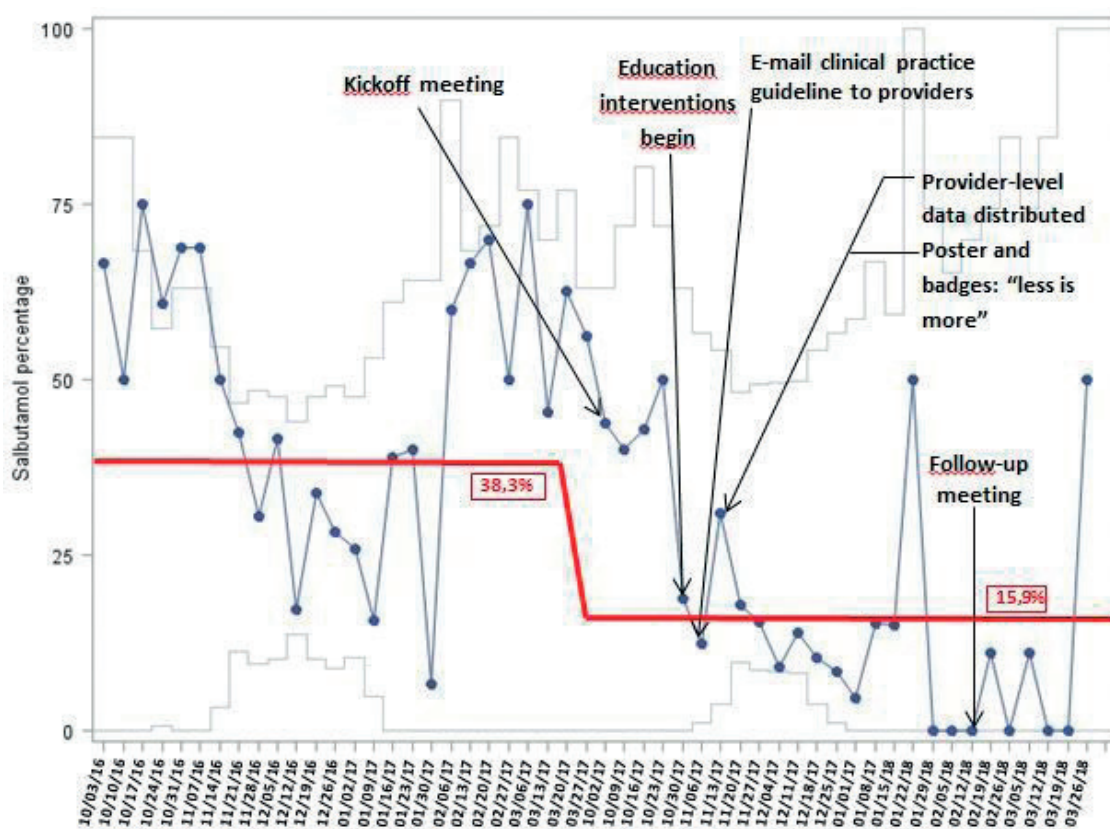


Figure 3 P chart showing decrease in the percentage of infants prescribed salbutamol in the primary care settings after implementation of the QI initiative. QI, quality improvement.

DISCUSSION

Our coordinated, multisite, multidisciplinary QI initiative significantly reduced the use of bronchodilators in children seen in PC settings and the ED for bronchiolitis without unintended consequences, such as hospitalisations, ED revisits, readmission or escalation of care in the PICU. To our knowledge, this is the first QI project in which researchers simultaneously implement improvement initiatives in PC and the corresponding hospital ED. Given that our baseline use is probably comparable with the current practice in other ED and PC settings, our study has implications for other similar health areas that want to undertake projects for the improvement in the management of AB.

Previous studies conducted in hospital settings have demonstrated the usefulness of implementing QI measures at a local level or with collaboration between different settings to improve the management of AB.^{14 19 20} A study conducted by Ralston *et al* to assess a collaborative multicentre strategy¹⁹ found a significant decrease in the use of bronchodilators and corticosteroids after the dissemination of the AAP guidelines and education through interactive webinars. Similarly, multifaceted educational bundles, such as the one described by Murch *et al*,²¹ can significantly improve adherence to guidelines. However, there is little knowledge about the use of pharmacotherapy and improvement initiatives for the management of bronchiolitis at the PC level. A study carried out in our area in 2017 showed a high use of bronchodilators and other medications in bronchiolitis in PC.⁷ In the same study, the authors showed that the implementation of a QI intervention was succes-

ful in reducing the use of pharmacotherapy in AB in PC settings. Nonetheless, they found that more than 30% of infants with AB continued to be treated with bronchodilators and other medications. A lack of knowledge of real-time data about the prescription of medications throughout AB season and the lack of communication between paediatricians working in PC settings can partially explain the difficulties of achieving a better result with the initiative undertaken.

The persistence of this high use of pharmacotherapy in our area was the main reason for carrying out the present study. Taking into account the experience accumulated during the previous improvement initiative, we planned a new QI cycle. For this new initiative, we decided to maintain the same objective, namely, to reduce the use of medications but incorporate new improvement measures. As has been observed in other disease processes, showing clinicians their performance data compared with peers likely positively influences their behaviour.^{22 23} In our study, the combination of having regular information on prescription data in the different PC settings and the ED and seeing individualised data may have effectively influenced clinician management decisions. Furthermore, initiatives to keep our project goals visible such as the placement of posters in the ED and PC centres and badges for staff uniforms with the project slogan 'Bronchiolitis, less is more' may have played a role in reducing the overuse of medication in AB.

Nonetheless, we think it is likely that the factor that has had the greatest impact on the results of our improvement initiative has been the collaboration between the ED and PC. It has been shown that

Table 1 Comparison of outcome measures for patients seen in the emergency department and patients seen in the primary care settings where the intervention was carried out in the preintervention and postintervention acute bronchiolitis seasons

	2016–2017 season	2017–2018 season	P value
Patients seen in the emergency department, n	1023	855	
Salbutamol received, n (%)	142; 13.8% (95% CI 11.8% to 16%)	78; 9.1% (95% CI 7.3% to 11.2%)	0.001
Epinephrine received, n (%)	107; 10.4% (95% CI 8.6% to 12.4%)	77; 9% (95% CI 7.2% to 11.1%)	0.36
Patients seen in primary care settings, n	658	534	
Salbutamol prescribed, n (%)	252; 38.3% (95% CI 34.6% to 42.0%)	85; 15.9% (95% CI 12.9% to 19.5%)	<0.001
Antibiotics prescribed, n (%)	195; 29.6% (95% CI 26.2% to 33.2%)	51; 9.5% (95% CI 7.2% to 12.5%)	<0.001
Corticosteroids prescribed, n (%)	85; 12.9% (95% CI 10.5% to 15.7%)	19; 3.5% (95% CI 2.2% to 5.7%)	<0.001

Table 2 Balance measures for episodes seen in the emergency department in the preintervention and postintervention acute bronchiolitis seasons

Total population of episodes seen in the emergency department	2016–2017 season n=1023	2017–2018 season n=855	P value
Age (months), mean (SD)	6.9 (5)	6.4 (4.5)	0.18
Acuity level I–II n (%)	63 (6.1)	58 (6.7)	0.58
Acuity level I–III n (%)	755 (73.8)	633 (74)	0.90
Mean length of stay (SD) (min)	241.7 (364.4)	223.6 (326.1)	0.005
Hospitalisation rate, n (%)	121 (11.8)	114 (13.3)	0.32
Intensive care unit admission rate, n (%)	47 (4.6)	43 (5)	0.74
Emergency department revisits, n (%)	155 (15.1)	140 (16.3)	0.43
Revisits with admission, n (%)	33 (3.2)	25 (2.9)	0.059
Episodes from primary care settings with intervention seen in the emergency department	2016–2017 season n=392	2017–2018 season n=333	P value
Age (months), mean (SD)	6.8 (4.9)	6.3 (4.5)	0.30
Acuity level I–II, n (%)	18 (4.7)	22 (6.6)	0.23
Acuity level I–III, n (%)	281 (71.6)	244 (72.8)	0.63
Mean length of stay (min) (SD)	214.3 (340.7)	208 (302.9)	0.49
Hospitalisation rate, n (%)	36 (9.1)	36 (10.8)	0.54
Intensive care unit admission rate, n (%)	15 (3.8)	12 (3.6)	0.82
Emergency department revisits, n (%)	57 (15)	54 (16.1)	0.82
Revisits with admission, n (%)	12 (3.1)	10 (2.9)	0.87

Data from the total number of episodes and episodes from the primary care settings in which the intervention was performed are shown separately.

a lack of consensus between different levels of healthcare increases variability in clinical practice.²⁴ Since bronchiolitis lasts a minimum of 1–2 weeks, it is not unusual for patients with this disease to consult several times in different settings. This can increase the likelihood that a medication will be finally prescribed in one of these consultations. We believe that the global agreement on not using medications has been decisive in the success of our initiative.

Given the seasonal nature of AB, the lack of a control group has been noted as a limitation in ascertaining whether results obtained after an intervention are due to the improvement measures taken between two AB seasons.²² For the present study, we obtained data on the prescription of salbutamol in health districts in which no interventions were performed and these show high use of salbutamol, similar to that found in our study prior to the implementation of the improvement measures. This fact reinforces the conclusion that the results of our study are likely to be attributable to the interventions performed. However, our study shows that the results obtained after the improvement initiative carried out in a referral hospital do not imply a change in clinical practice in their geographical area of influence. In fact, despite the low use of salbutamol in the ED, PC settings without the interventions continued to have a high salbutamol prescription rate. This phenomenon has previously been described in the literature in relation to other disease processes. For example, while some studies have shown a decrease in the use of CT in paediatric head trauma in some North American hospitals,²⁵ another reflects the lack of changes across the whole country in the same period of time.²⁶

Limitations

Our study has various limitations. First of all, it only included two PC health districts and differences between these and those of other healthcare systems could lead to the same interventions having different outcomes elsewhere. Second, since we only obtained data on drug prescriptions for at-home use and did not investigate the potential administration of bronchodilators at the time of the PC visit, we may have underestimated pharmacological treatment overall. We believe that this potential underestimation would not, however, affect the primary outcome of these interventions, which is the decrease in prescription. Third, we did not review patient health records to assess whether clinicians used the McConnochie criteria for the diagnosis of AB,²⁷ as recommended by the established protocol, and hence, differences between professionals in the

diagnostic criteria applied could have led to differences in individual prescription rates. Lastly, fewer patients were diagnosed with bronchiolitis and more with asthma in the postintervention period. This fact could indicate a change in the diagnostic criteria of paediatricians and explain part of our results. Although some first wheezing episodes could be diagnosed with asthma, to justify bronchodilator treatment, we believe that repeated episodes of wheezing diagnosed with bronchiolitis in the preintervention period are more likely to be diagnosed with asthma in the postintervention period. It is important to note that one of the interventions carried out was to update the diagnostic criteria of bronchiolitis.

Future directions

To achieve greater applicability in different healthcare environments, future improvement projects should include the experience of families and professionals with the global process of bronchiolitis.²⁸

Future research should explore provider attitudes, differences in acceptability by provider type, unintended consequences and the effectiveness of the collaboration between different steps of healthcare. Finally, studies in which researchers use implementation methodology are needed to determine which of our interventions were most effective in changing provider behaviour for which patients and through which mechanisms.²⁹

CONCLUSIONS

Our QI intervention significantly reduced the prescription and overuse of medications in bronchiolitis in our health area without unintended consequences for patients. Collaboration between PC and ED appears to be an important factor for success.

Twitter Elizabeth L Corbett @LizCorbett17

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ORCID iDs

Santiago Mintegi <http://orcid.org/0000-0002-2342-8881>

Javier Benito <http://orcid.org/0000-0003-1548-7408>

REFERENCES

- Meissner HC. Viral bronchiolitis in children. *N Engl J Med* 2016;374:62–72.
- National Institute for Health and Care Excellence. Bronchiolitis: diagnosis and management of bronchiolitis in children. Clinical guideline NG9. London: National Institute for Health and Clinical Excellence; 2015. <https://www.nice.org.uk/Guidance/NG9>
- Friedman JN, Rieder MJ, Walton JM, et al. Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age. *Paediatr Child Health* 2014;19:485–91.
- Ochoa Sangrador C, González de Dios J, Research Group of the aBREVIA Do Project. Overuse of bronchodilators and steroids in bronchiolitis of different severity: bronchiolitis-study of variability, appropriateness, and adequacy. *Allergol Immunopathol*
- Florin TA, Byczkowski T, Ruddy RM, et al. Variation in the management of infants hospitalized for bronchiolitis persists after the 2006 American Academy of pediatrics bronchiolitis guidelines. *J Pediatr* 2014;165:786–92.
- Elenius V, Berghöj E, Koponen P, et al. Marked variability observed in inpatient management of bronchiolitis in three Finnish hospitals. *Acta Paediatr* 2017;106:1512–8.
- Montejo Fernández M, Benito Manrique I, Montiel Eguía A, et al. An initiative to reduce the use of unnecessary medication in infants with bronchiolitis in primary care. *Anales de Pediatr* 2019;90:19–25.
- Parikh K, Hall M, Teach SJ. Bronchiolitis management before and after the AAP guidelines. *Pediatrics* 2014;133:e1–7.
- Akenroye AT, Baskin MN, Samnaliev M, et al. Impact of a bronchiolitis guideline on ED resource use and cost: a segmented time-series analysis. *Pediatrics* 2014;133:e227–34.
- Mittal V, Hall M, Morse R, et al. Impact of inpatient bronchiolitis clinical practice guideline implementation on testing and treatment. *J Pediatr* 2014;165:570–6.
- Benhamida M, Bihouet T, Verstraete M, et al. Retrospective audit of guidelines for investigation and treatment of bronchiolitis: a French perspective. *BMJ Paediatr Open* 2017;1:e000089.
- Hartling L, Scott-Findlay S, Johnson D, et al. Bridging the gap between clinical research and knowledge translation in pediatric emergency medicine. *Acad Emerg Med* 2007;14:968–77.
- Rodríguez-Martínez CE, Sossa-Briceno MP, Acuña-Cordero R. Quality assessment of acute viral bronchiolitis clinical practice guidelines. *J Eval Clin Pract* 2017;23:37–43.
- Ralston S, Connick A, Nichols E, et al. Effectiveness of quality improvement in hospitalization for bronchiolitis: a systematic review. *Pediatrics* 2014;134:571–81.
- Schondelmeyer AC, Simmons JM, Statile AM, et al. Using quality improvement to reduce continuous pulse oximetry use in children with wheezing. *Pediatrics* 2015;135:e1044–51.
- Ralston S, Parikh K, Goodman D. Benchmarking overuse of medical interventions for bronchiolitis. *JAMA Pediatr* 2015;169:805–6.
- Zamorá-Flores D, Busen NH, Smout R, et al. Implementing a clinical practice guideline for the treatment of bronchiolitis in a high-risk Hispanic pediatric population. *J Pediatr Health Care* 2015;29:169–80.
- Provost LP, Murray S. The health care data guide: learning from data for improvement. 1st ed. San Francisco, CA: Jossey-Bass; 2011.
- Ralston SL, Garber MD, Rice-Conboy E, et al. A multicenter collaborative to reduce unnecessary care in inpatient bronchiolitis. *Pediatrics* 2016;137:e20150851.
- Musmann GM, Lossius M, Wasif F, et al. Multisite emergency department inpatient collaborative to reduce unnecessary bronchiolitis care. *Pediatrics* 2018;141:e20170830.
- Murch H, Oakley J, Pierrepont M, et al. Using multifaceted education to improve management in acute viral bronchiolitis. *Arch Dis Child* 2015;100:654–8.
- Tyler A, Krack P, Bakel LA, et al. Interventions to reduce over-utilized tests and treatments in bronchiolitis. *Pediatrics* 2018;141:e20170485.
- Jamvedt G, Young JM, Kristoffersen DT, et al. Does telling people what they have been doing change what they do? A systematic review of the effects of audit and feedback. *Qual Saf Health Care* 2006;15:433–6.
- González de Dios J, Ochoa Sangrador C, Research group of the aBREVIA Do project. Study of variability in the management of acute bronchiolitis in Spain in relation to age of patients national multicenter study (aBREVIA Do project). *An Pediatr* 2010;72:4–18.
- Jennings RM, Burtner JJ, Pellicer JF, et al. Reducing head CT use for children with head injuries in a community emergency department. *Pediatrics* 2017;139:e20161349.
- Burstein B, Upton JEM, Terra HF, et al. Use of CT for head trauma: 2007–2015. *Pediatrics* 2018;142:e20180814.
- Bronchiolitis MCM. What's in the name? *Am J Dis Child* 1983;137:11–13.
- Cunningham S, Pinnock H. Implementation science takes baby steps in infants with bronchiolitis. *Thorax* 2018;73:599–600.
- Haskell L, Tavender EJ, Wilson C, et al. Implementing evidence-based practices in the care of infants with bronchiolitis in Australian acute care settings: study protocol for a cluster randomised controlled study. *BMC Pediatr* 2018;18:218.

Medidas de saúde pública para COVID-19: uma redução dos internamentos hospitalares por agudização de DPOC

Jing Yuan Tan,¹ Edwin Philip Conceicao,² Liang En Wee,³ Xiang Ying Jean Sim,^{2,3} Indumathi Venkatachalam^{2,3}

¹Department of Internal Medicine, Singapore General Hospital, Singapore

²Department of Infection Prevention and Epidemiology, Singapore General Hospital, Singapore

³Department of Infectious Diseases, Singapore General Hospital, Singapore

Correspondence to

Dr Jing Yuan Tan, Singapore General Hospital, 169608, Singapore; jingyuan.tan@mohh.com.sg

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RESUMO

As hospitalizações por agudização aguda de DPOC (EADPOC) implicam uma morbidade e mortalidade significativas. As infecções respiratórias virais (IRV) são a causa mais comum de EADPOC e estão associadas a resultados clínicos inferiores. Durante a pandemia de COVID-19, as medidas de saúde pública, como o distanciamento social e a utilização de máscaras universal, foram originalmente implementadas para reduzir a transmissão do SARS-CoV-2. Estas medidas de saúde pública também foram subsequentemente observadas para reduzir a transmissão de outras IRV comuns em circulação. Neste estudo, relatamos uma diminuição significativa e sustentada das admissões hospitalares para todas as EADPOC, bem como para as IRV associadas à EADPOC, que coincidiu com a introdução de medidas de saúde pública durante a pandemia da COVID-19.

INTRODUCTION

COPD is the third leading cause of global mortality.¹ Preventive measures, including smoking cessation, pulmonary rehabilitation and vaccinations, are key strategies to reduce exacerbations and hospitalisations. Common respiratory viral infections (RVIs) are common triggers of acute exacerbations of COPD (AECOPD) and contribute significantly to hospitalisations.² Thus reducing viral exacerbations can lead to improved outcomes in patients with COPD. In Singapore, various public health measures including hygiene reinforcement, social distancing and compulsory mask-wearing were implemented during the COVID-19 pandemic to reduce SARS-CoV-2 transmission. These measures were effective in mitigating community transmission of SARS-CoV-2 and in addition, other common circulating RVIs.³ We thus sought to assess if these measures would also potentially be associated with a reduction in hospitalisations for AECOPD, in particular exacerbations associated with common RVIs.

METHODS

Anonymised epidemiological data on AECOPD admissions was obtained from our institution's electronic database using discharge diagnosis codes. The total number of AECOPD admissions and the proportion of those admissions who tested positive for a concomitant RVI over a 6-month period during the COVID-19 pandemic (February 2020 to July 2020) were compared against a 2-year prepandemic period (January 2018 to January 2020). In clinical practice, patients presenting with clinical syndromes compatible with a viral exacerbation of COPD (eg, normal serum procalcitonin) were tested for common RVIs using a 16-target respiratory virus multiplex PCR assay (RV-16) on respiratory specimens, at the primary physician's discretion. Trends in AECOPD admissions and the proportion of AECOPD admissions who were tested and had a PCR-positive RVI were compared in the prepandemic and pandemic periods, using t-test and χ^2 test, respectively. The incidence of PCR-positive RVI among AECOPD admissions during the prepandemic and pandemic periods was compared using the incidence rate ratio method.

RESULTS

The introduction of public health measures during the COVID-19 pandemic coincided with a significant decrease in admissions for AECOPD over a sustained 6-month period, as well as a decrease in concomitant

PCR-positive RVI-associated AECOPD admissions (figure 1). Prepandemic, our hospital saw an average of 92 (SD 18) AECOPD admissions per month; this decreased by more than 50% to 36 (SD 6) admissions per month during the pandemic period (February–July 2020) ($p<0.001$). During the pandemic, the proportion of AECOPD admissions tested for common RVIs increased substantially (prepandemic: 60% vs pandemic: 98%). Elevated vigilance for respiratory symptoms during the ongoing pandemic likely drove the increase in testing. Despite the substantial increase in testing, the incidence of PCR-positive RVI among AECOPD admissions dropped significantly during the pandemic period. The incidence rate of PCR-positive RVI was 106 cases per 1000 AECOPD admissions (23 cases, 216 admissions) during the pandemic, compared with 304 cases per 1000 AECOPD admissions prepandemic (701 cases, 2300 admissions); the decline was statistically significant (incidence rate ratio=0.35, 95% CI 0.22 to 0.53, $p<0.001$).

Prepandemic, close to half of AECOPD admissions tested had a PCR-positive RVI (48.8%, 701/1437). During the pandemic period, only 10.8% (23/212) of AECOPD admissions had a PCR-positive RVI; the decline was statistically significant (OR=7.8, 95% CI 5.0 to 12.8, $p<0.001$).

DISCUSSION

According to the 2020 GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines, COPD exacerbations associated with hospitalisations place patients in a more severe group. Frequent exacerbations lead to increased mortality, accelerated lung function decline and poor quality of life.⁴ Detection of a respiratory virus in respiratory specimens in both stable COPD and in AECOPD has been shown to be associated with worse clinical outcomes.^{5,6} As not all common RVIs are preventable with vaccines, simple public health measures to reduce community transmission of RVIs especially among vulnerable individuals may be important. The impetus for widespread adoption of public health measures, including social distancing and universal masking, during a pandemic provided a unique opportunity to observe the potential impact of such measures on AECOPD admissions. A significant decline in AECOPD admissions and incidence of PCR-positive RVI was observed over a 6-month period during the COVID-19 pandemic, coinciding with the introduction of these public health measures. Even after the nationwide lockdown was lifted from June 2020, our institution observed zero cases of COPD admissions with concomitant PCR-positive RVI, an observation unprecedented in the preceding 2 years of surveillance.

Our study's limitations are as follows. It is possible that a reduction in admissions could be driven by a reluctance to present to hospital during the COVID-19 pandemic. Seasonality may also result in potential variations in RVI rates; however while seasonality is prominent in temperate countries, in a tropical country such as Singapore, seasonality is only observed for specific viral pathogens like influenza, and even then, does not follow the annual trend seen in temperate regions.⁷ The singlecentre nature of our study may also preclude generalisability. In addition, only hospitalisations but not outpatient attendances were included. Nonetheless, hospitalisation episodes are more significant in the prognosis of patients with COPD, highlighting the value of our observation.

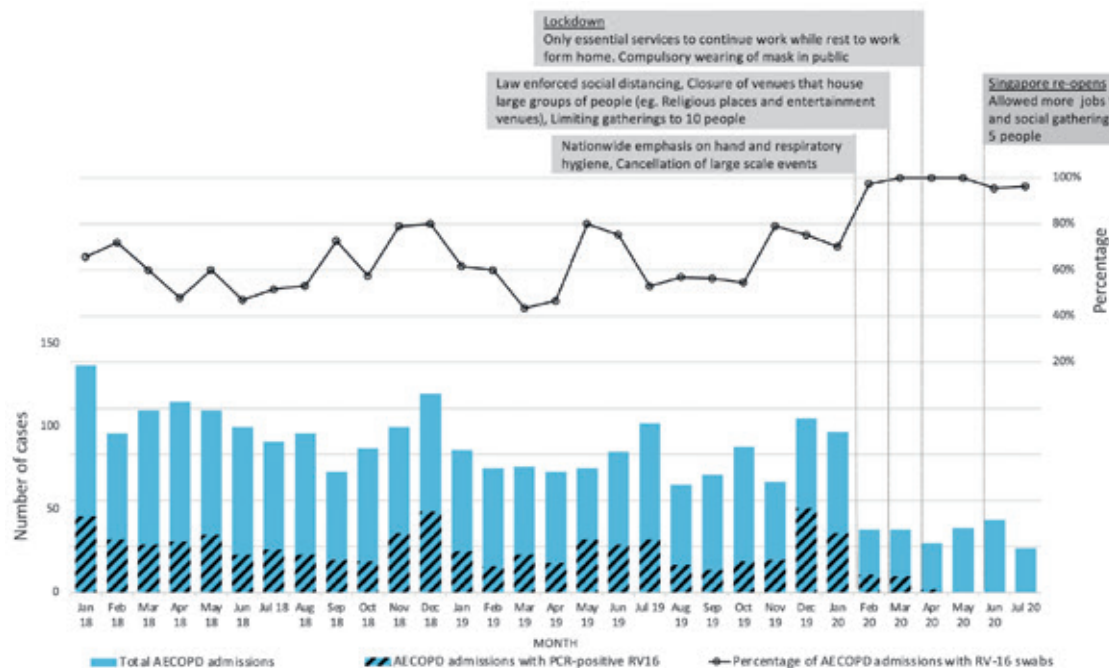


Figure 1 Trend of AECOPD admissions and proportion with PCR-positive RV-16. Line graph depicts the percentage of AECOPD admissions tested for respiratory viruses. The standard respiratory virus multiplex panel (RV-16) at our institution included: respiratory syncytial virus A/B, influenza A/B, parainfluenza viruses 1–4, metapneumovirus, rhinovirus A/B/C, human coronavirus OC43/229E/NL63, adenovirus, human enterovirus, human bocavirus 1–4.

In conclusion, we report a significant reduction in AECOPD admissions and RVI-associated AECOPD admissions coinciding with the widespread adoption of public health measures during a pandemic. This reduction was sustained even after the reversal of community-wide lockdown measures. The complementary role of simple preventive measures such as wearing of face coverings, hand hygiene and social distancing in reducing AECOPD admissions deserves further investigation. These public health measures may have an important role in the postpandemic era, for population health outcomes especially for patients with COPD.

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REFERENCES

- Linden D, Guo-Parke H, Coyle PV, et al. Respiratory viral infection: a potential "missing link" in the pathogenesis of COPD. *Eur Respir J* 2019;28:180063.
- Hewitt R, Farne H, Ritchie A, et al. The role of viral infections in exacerbations of chronic obstructive pulmonary disease and asthma. *Thorax* 2016;71:158–74.
- Tan JY, Conceicao EP, Sim XY, et al. Public health measures during COVID-19 pandemic reduced hospital admissions for community respiratory viral infections. *J Hosp Infect* 2020;106:387–9.
- Mathioudakis AG, Janssens W, Sivapalan P, et al. Acute exacerbations of chronic obstructive pulmonary disease: in search of diagnostic biomarkers and treatable traits. *Thorax* 2020;75:520–7.
- Wilkinson TMA, Aris E, Bourne S, et al. A prospective, observational cohort study of the seasonal dynamics of airway pathogens in the aetiology of exacerbations in COPD. *Thorax* 2017;72:919–27.
- Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1618–23.
- Chew FT, Dorasingham S, Ling AE, et al. Seasonal trends of viral respiratory tract infections in the tropics. *Epidemiol Infect* 1998;121:121–28.

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Fatores de risco no início de vida para limitação reversível e irreversível dos débitos ventilatórios em jovens adultos: resultados da coorte de nascimento BAMSE

Gang Wang,^{1,2,3} Inger Kull,^{2,3,4} Anna Bergström,^{2,5} Jenny Hallberg,^{3,4} Petra Um Bergström,^{3,4} Stefano Guerra,^{6,7} Goran Pershagen,^{2,5} Olena Gruzieva,^{2,5} Marianne van Hage,⁸ Antonios Georgelis,^{2,5} Christer Janson,⁹ Anders Lindén,^{2,10} Erik Melén^{2,3,4}

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For numbered affiliations see end of article.

Correspondence to

Dr Erik Melén, Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm 118 83, Sweden; erik.melen@ki.se

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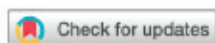
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RESUMO

O nosso objetivo foi determinar a prevalência e os fatores de risco no início de vida para limitação reversível e irreversível dos débitos ventilatórios em jovens adultos da população em geral. Entre os jovens adultos na faixa dos 20 anos, a prevalência foi de 5,3% para a limitação reversível dos débitos ventilatórios e 2,0% para a limitação irreversível dos débitos ventilatórios. Embora a asma parental fosse o único fator de risco para o desenvolvimento da limitação reversível dos débitos ventilatórios, os fatores de risco para o desenvolvimento de limitação irreversível dos débitos ventilatórios foram asma atual, infecções do trato respiratório infantil e asma e exposição à poluição atmosférica.

It has been shown that impaired lung function in children and young adults is associated with an increased risk of chronic obstructive pulmonary disease (COPD) later in life.^{1,2} Recently, airflow limitation defined as pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) below the lower limit of normal (LLN) was observed in 4% of adults aged 20–29 years who have less than 5 pack-years tobacco load, and up to 7% in participants who have 5 pack-years or more tobacco load.³ However, few published studies addressed reversible airflow limitation and irreversible airflow limitation in young adults. Given this, we aimed to determine the prevalence and early-life risk factors for reversible airflow limitation and irreversible airflow limitation in young adults from the general population.

A total of 1932 participants in the population-based birth cohort Barn/Children, Allergy, Milieu, Stockholm, Epidemiology (BAMSE) performed valid pre-BD and post-BD lung function measurements at the 24-year follow-up.⁴ Lung function was tested according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria as previously described.⁶ Post-BD lung function was tested 15 min after administration of 400 µg salbutamol. 'Normal lung function' was defined as pre-BD and post-BD FEV₁/FVC ≥ LLN,⁷ 'Reversible airflow limitation' as pre-BD FEV₁/FVC < LLN but post-BD FEV₁/FVC ≥ LLN, and 'Irreversible airflow limitation' as pre-BD and post-BD FEV₁/FVC < LLN. ORs and 95% CIs for risk factors in relation to reversible airflow limitation or irreversible airflow limitation, selected based on previous literature and availability in BAMSE, were estimated using multivariable logistic regression in R (V.4.0.2).

The prevalence of reversible airflow limitation was 5.3% (n=103, 95%CI 4.3% to 6.3%), and

irreversible airflow limitation 2.0% (n=39, 95%CI 1.4% to 2.6%) at the 24-year follow-up. Forty-nine per cent reported respiratory symptoms in those with irreversible airflow limitation compared with 25% in those with normal lung function (table 1). In addition, participants in the irreversible airflow limitation group also reported more cough, but not more mucus production, during winter mornings. Besides, there were reports of more respiratory symptoms (defined as troublesome breathing, chest tightness or wheezing) and pneumonia events during the last 12 months in the irreversible airflow limitation group. However, no such differences were observed for the groups with reversible airflow limitation and normal lung function. There were lower pre-BD FEV₁ and post-BD FEV₁ (by design, online supplemental table E1), higher pre-BD FVC and post-BD FVC, and higher reversibility (change in FEV₁ and change in FEV₁ % baseline) in the reversible and irreversible airflow limitation groups compared with the group with normal lung function. Fifteen and 2.9% of participants with irreversible and reversible airflow limitation had post-BD FEV₁ lower than LLN, respectively, compared with 1.5% in the group with normal lung function (online supplemental table E1). No substantial difference was observed for other variables, except higher body mass index (BMI) was observed in participants with irreversible airflow limitation (table 1). In logistic regression models adjusted for age, gender and BMI, several indicators of early life infections and respiratory diseases, environmental exposures and current asthma were risk factors associated with irreversible airflow limitation (table 2). In mutually adjusted analyses, respiratory syncytial virus (RSV) infection/pneumonia during infancy, nitrogen oxide (NO_x) exposure during age 0–1 years, childhood asthma during age 0–4 years and current asthma were independent risk factors for irreversible airflow limitation (table 3). For reversible airflow limitation, parental asthma and childhood asthma during age 0–4 and 8–12 years, NO_x exposure during age 8–12 years and current asthma were associated factors. In mutually adjusted analyses, parental asthma alone was an independent risk factor for reversible airflow limitation.

In summary, we found the overall prevalence of reversible and irreversible airflow limitation to be rather high (5.3% and 2.0%, respectively), considering the young age of the participants. Individuals with irreversible airflow limitation more often reported current respiratory symptoms and pneumonia compared with those

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Table 1 Characteristics of cohort participants with Irreversible airflow limitation or Reversible airflow limitation and normal lung function*

	Irreversible airflow limitation (N=39)	Reversible airflow limitation (N=103)	Normal lung function (N=1790)	P value	
				Irreversible airflow limitation versus normal lung function	Reversible airflow limitation versus normal lung function
Age, years, mean (SD)	22.4 (0.5)	22.4 (0.5)	22.4 (0.5)	0.7387	0.5593
Sex, female, n (%)	19 (48.7)	58 (56.3)	1042 (58.2)	0.2346	0.7037
BMI, kg/m ² , mean (SD)	24.9 (5.9)	23.2 (3.0)	23.1 (3.8)	0.0060	0.9549
Education, n (%)				0.1506	0.7524
Secondary school	20 (51.3)	62 (60.2)	1118 (62.6)		
High school	9 (23.1)	23 (22.3)	405 (22.7)		
University	10 (25.6)	18 (17.5)	264 (14.8)		
Active childhood smoking, n (%)				0.2804	0.8711
Never	23 (59.0)	70 (68.0)	1200 (67.2)		
Ever	16 (41.0)	33 (32.0)	586 (32.8)		
Tobacco consumption (pack-years), median (IQR)	1.1 (0.1 to 1.6)	1.0 (0.1 to 2.3)	0.4 (0.1 to 1.7)	0.4504 †	0.3609 †
Respiratory health events					
Cough during winter morning, n (%)	9 (23.1)	11 (10.8)	139 (7.9)	0.0006	0.3686
Mucus production during winter morning, n (%)	6 (15.8)	18 (17.8)	257 (14.6)	0.8319	0.4999
Respiratory symptoms, n (%)	19 (48.7)	34 (33.0)	451 (25.2)	0.0009	0.0791
Pneumonia in the last 12 months, n (%)	4 (10.3)	3 (3.0)	44 (2.5)	0.0183‡	0.7387‡
Sensitisation at age 24 years					
Sensitisation to airborne allergens, n (%)	18 (46.2)	36 (35.6)	767 (43.5)	0.7414	0.1207
Sensitisation to food allergens, n (%)	5 (12.8)	10 (9.9)	153 (8.7)	0.3826‡	0.6736
Reversibility test					
Change in FEV ₁ , mL, median (IQR)	243 (156 to 360)	273 (192 to 373)	111 (50 to 185)	<0.0001†	<0.0001†
Change in FEV ₁ % baseline, %, median (IQR)	7.3 (4.2 to 10.2)	7.7 (5.1 to 9.9)	2.8 (1.3 to 4.6)	<0.0001†	<0.0001†
Blood different cell count, × 10 ⁹ /L					
Neutrophils, mean (SD)	3.86 (1.5)	3.51 (1.37)	3.71 (1.4)	0.5358	0.1734
Eosinophils, median (IQR)	0.10 (0.1 to 0.2)	0.10 (0.0 to 0.2)	0.10 (0.0 to 0.2)	0.0529†	0.7534†

*Details about the definitions of health outcomes and covariates are provided in the online supplemental file.

†Based on Kruskal-Wallis rank sum test.

‡Based on Fisher's exact test.

BMI, body mass index; FEV₁, forced expiratory volume in 1 s.**Table 2** Logistic regression model reversible and irreversible airflow limitation adjusted for age, gender, and body mass index*

	Normal lung function		Reversible airflow limitation		Irreversible airflow limitation	
	No of individuals/cases	OR (95%CI)	No of individuals/cases	OR (95%CI)	No of individuals/cases	OR (95%CI)
Parental education, primary school/high school versus university	1787/774	1 (Reference)	102/40	0.85 (0.56 to 1.28)	39/17	0.98 (0.51 to 1.86)
Maternal smoking during pregnancy	1789/197	1 (Reference)	103/14	1.26 (0.70 to 2.27)	39/5	1.13 (0.44 to 2.96)
Parental asthma	1776/342	1 (Reference)	103/36	2.24 (1.47 to 3.42)	39/7	0.9 (0.39 to 2.07)
Preterm birth	1790/95	1 (Reference)	103/5	0.91 (0.36 to 2.28)	39/3	1.42 (0.43 to 4.71)
Parental smoking during childhood	1790/526	1 (Reference)	103/33	1.13 (0.74 to 1.73)	39/12	1.02 (0.51 to 2.05)
Active childhood smoking, ever versus never	1786/586	1 (Reference)	103/33	0.97 (0.63 to 1.48)	39/16	1.40 (0.73 to 2.69)
RSV infection/pneumonia during infancy	1745/125	1 (Reference)	99/3	0.40 (0.13 to 1.29)	39/9	3.72 (1.71 to 8.11)
Pneumonia during age 0–4 years	1772/189	1 (Reference)	100/7	0.62 (0.29 to 1.37)	39/9	2.42 (1.12 to 5.23)
Childhood asthma during age 0–4 years	1772/179	1 (Reference)	100/17	1.81 (1.04 to 3.13)	38/11	3.26 (1.57 to 7.78)
Childhood asthma during age 4–8 years	1606/99	1 (Reference)	91/10	1.86 (0.93 to 3.70)	35/4	1.73 (0.58 to 5.11)
Childhood asthma during age 8–12 years	1589/108	1 (Reference)	93/12	1.98 (1.04 to 3.76)	36/3	1.08 (0.32 to 3.64)
Childhood asthma during age 12–16 years	1560/104	1 (Reference)	94/11	1.84 (0.95 to 3.58)	36/4	1.58 (0.54 to 4.68)
Current asthma	1783/210	1 (Reference)	100/17	2.32 (1.43 to 3.77)	39/11	2.75 (1.34 to 5.66)
NO _x concentration higher than the median†						
Age 0–1 years	1767/911	1 (Reference)	103/45	0.72 (0.48 to 1.08)	39/28	2.61 (1.28 to 5.35)
Age 1–4 years	1640/859	1 (Reference)	88/39	0.72 (0.47 to 1.11)	37/24	1.74 (0.88 to 3.44)
Age 4–8 years	1488/742	1 (Reference)	81/38	0.88 (0.56 to 1.38)	34/21	1.71 (0.85 to 3.46)
Age 8–12 years	1637/832	1 (Reference)	90/36	0.64 (0.41 to 0.98)	37/22	1.53 (0.78 to 2.99)
Age 12–16 years	1453/737	1 (Reference)	82/38	0.82 (0.53 to 1.29)	33/22	2.19 (1.04 to 4.62)
PM ₁₀ concentration higher than the median‡						
Age 0–1 years	1767/914	1 (Reference)	103/47	0.78 (0.52 to 1.17)	39/29	2.96 (1.42 to 6.18)
Age 1–4 years	1640/840	1 (Reference)	88/43	0.89 (0.58 to 1.37)	37/26	2.39 (1.16 to 4.92)
Age 4–8 years	1488/759	1 (Reference)	81/39	0.91 (0.58 to 1.42)	34/22	1.79 (0.88 to 3.67)
Age 8–12 years	1637/827	1 (Reference)	90/36	0.65 (0.42 to 1.00)	37/22	1.54 (0.79 to 3.02)
Age 12–16 years	1453/742	1 (Reference)	82/36	0.76 (0.48 to 1.19)	33/21	1.85 (0.89 to 3.84)

*Details about the definitions of the covariates are provided in the online supplemental file.

†The median NO_x concentration for ages 0–1, 1–4, 4–8, 8–12 and 12–16 years were 29.16, 24.21, 18.31, 13.66 and 11.16 µg/m³.‡The median PM₁₀ concentration for ages 0–1, 1–4, 4–8, 8–12, and 12–16 years were 14.46, 13.28, 13.33, 13.34 and 12.24 µg/m³.NO_x, nitrogen oxides; PM₁₀, particulate matter with aerodynamic diameter <10 µm; RSV, respiratory syncytial virus.

Table 3 Mutually adjusted analyses for reversible and irreversible airflow limitation which included age, gender, body mass index and other related factors*

	Normal lung function		Irreversible airflow limitation	
	No of individuals/cases	OR (95%CI)	No of individuals/cases	OR (95%CI)
NOx concentration during age 0–1 yearst, high versus low	1261/651	1 (Reference)	29/22	3.08 (1.11 to 8.51)
NOx concentration during age 12–16 yearst, high versus low	1261/637	1 (Reference)	29/21	2.12 (0.82 to 5.46)
RSV infection/pneumonia during infancy	1261/84	1 (Reference)	29/8	3.59 (1.41 to 9.14)
Childhood asthma during age 0–4 years	1261/127	1 (Reference)	29/8	3.36 (1.22 to 9.24)
Childhood asthma during age 4–8 years	1261/78	1 (Reference)	29/2	0.32 (0.06 to 1.81)
Childhood asthma during age 8–12 years	1261/82	1 (Reference)	29/1	0.16 (0.02 to 1.43)
Childhood asthma during age 12–16 years	1261/78	1 (Reference)	29/3	1.31 (0.32 to 5.44)
Current asthma	1261/144	1 (Reference)	29/7	3.51 (1.22 to 10.15)
Variables	Normal lung function		Reversible airflow limitation	
Parental asthma	1317/253	1 (Reference)	77/28	2.17 (1.31 to 3.58)
NOx concentration during age 8–12 yearst, high versus low	1317/654	1 (Reference)	77/34	0.82 (0.51 to 1.32)
Childhood asthma during age 0–4 years	1317/137	1 (Reference)	77/14	1.37 (0.68 to 2.75)
Childhood asthma during age 4–8 years	1317/84	1 (Reference)	77/9	0.92 (0.36 to 2.34)
Childhood asthma during age 8–12 years	1317/88	1 (Reference)	77/10	1.22 (0.50 to 2.97)
Childhood asthma during age 12–16 years	1317/87	1 (Reference)	77/10	1.21 (0.51 to 2.86)
Current asthma	1317/154	1 (Reference)	77/16	1.49 (0.72 to 3.11)

Details about the definitions of covariates are provided in the online supplemental file.

†The median NO_x concentration for ages 0–1, 8–12 and 12–16 years were 29.16, 13.66 and 11.16 µg/m³.

NO_x, nitrogen oxides; RSV, respiratory syncytial virus.

with normal lung function. Besides, more severe lung function impairments were observed in individuals with irreversible airflow limitation. Thus, there was a substantial disease burden in participants with irreversible airflow limitation. Results from previous epidemiology studies demonstrate that abnormal lung development plays an important role in the development of COPD and a substantial proportion of subjects diagnosed with COPD after age 50 could be traced back to a relatively low peak lung function in their 20s.⁸ Our current findings extend those results by demonstrating that irreversible airflow limitation is present in young adults. This was observed despite most of them being nonsmokers, and ever-smokers having smoked on average less than one pack-year. Moreover, although only 28% of the irreversible airflow limitation subjects were classified as having current asthma, enhanced airway reversibility was observed, which suggests that, at this early stage of disease, reversibility is to some extent present.

In our study, early-life respiratory infections (RSV infection/pneumonia) and exposure to air pollutants, as well as childhood asthma, were identified as strong risk factors for irreversible airflow limitation. Given that air pollution levels in Stockholm are comparatively low by international standards, this makes the current findings alarming in a global context. Early risk factors may influence lung function development in a negative manner that will likely track with age,⁹ and in the current study, these early lung insults were even stronger risk factors for irreversible airflow limitation than smoking exposure in childhood and active smoking in adolescence. Thus, early-life exposure to air pollutants emerges as an important risk factor, known to be associated with not only lung development,⁶ but also with childhood pneumonia¹⁰ and asthma.¹¹

In our study, the only identified independent risk factor for reversible airflow limitation was parental asthma, which suggests that the reversible airflow limitation phenotype relates primarily to asthma heredity, rather than to impaired lung development. Our study has the drawback of a relatively small irreversible airflow limitation sample size and only around 50% of the initial 4089 cohort participants provided pre-BD and post-BD spirometry data at 24 years of age. However, no selection bias could be identified so far in the BAMSE cohort.⁴

In conclusion, this study forwards evidence that among young adults in their 20s, the prevalence was 5.3% for reversible airflow limitation and 2.0% for irreversible airflow limitation. While parental asthma emerges as the only risk factor

for development of reversible airflow limitation, the risk factors for development of irreversible airflow limitation were current asthma, childhood respiratory tract infections and asthma, and exposure to air pollution.

Author affiliations

¹Department of Integrated Traditional Chinese and Western Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China

²Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

³Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

⁴Sachs' Children's Hospital, Stockholm, Sweden

⁵Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden

⁶Asthma and Airway Disease Research Center, The University of Arizona, Tucson, Arizona, USA

⁷ISGLOBAL, Barcelona, Spain

⁸Medicine Solna, Division of Immunology and Allergy, Karolinska Institutet, Stockholm, Sweden

⁹Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

¹⁰Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Stockholm, Sweden

Contributors JH, AL and EM designed the study and outlined the contents of the manuscript. GW was responsible for the practical conduct of the study, including the planning, coordination and analyses of the data, and the writing the manuscript under the supervision by EM. JH had overall responsibility for the lung function measurements at 24 years of age. GP and OG had overall responsibility for the air pollution data. PUB, CJ, MvH, AG, AB, SG and IK revised the work critically for the content. All authors contributed to the interpretation of the data and approved the final manuscript prior to its submission.

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Competing interests EM reports personal fees from Sanofi, Chiesi and AstraZeneca, outside the submitted work.

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ORCID iDs

Stefano Guerra <http://orcid.org/0000-0001-7218-3246>

Christer Janson <http://orcid.org/0000-0001-5093-6980>

REFERENCES

- Agusti A, Faner R. Copd beyond smoking: new paradigm, novel opportunities. *Lancet Respir Med* 2018;6:324–6.
- Melén E, Guerra S, Hallberg J, et al. Linking COPD epidemiology with pediatric asthma care: implications for the patient and the physician. *Pediatr Allergy Immunol* 2019;30:589–97.
- Çolak Y, Afzal S, Nordestgaard BG, et al. Prevalence, characteristics, and prognosis of early chronic obstructive pulmonary disease. The Copenhagen general population study. *Am J Respir Crit Care Med* 2020;201:671–80.
- Melén E, Bergström A, Kull I, et al. Male sex is strongly associated with IgE sensitization to airborne but not food allergens: results up to age 24 years from the BAMSE birth cohort. *Clin Transl Allergy* 2020;10:15.
- Wang G, Hallberg J, Bergström PU, et al. Assessment of chronic bronchitis and risk factors in young adults: results from BAMSE. *Eur Respir J* 2020.
- Schultz ES, Hallberg J, Bellander T, et al. Early-Life exposure to traffic-related air pollution and lung function in adolescence. *Am J Respir Crit Care Med* 2016;193:171–7.
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-Ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
- Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535–44.
- Stern DA, Morgan WJ, Wright AL, et al. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370:758–64.
- Darrow LA, Klein M, Flanders WD, et al. Air pollution and acute respiratory infections among children 0–4 years of age: an 18-year time-series study. *Am J Epidemiol* 2014;180:968–77.
- Gehring U, Wijga AH, Hoek G, et al. Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study. *Lancet Respir Med* 2015;3:933–42.



UMA TRIPLA
ASSOCIAÇÃO.
UMA ÚNICA TOMA³.
Um novo fôlego na DPOC.



LAMA | LABA | ICS



1 INALAÇÃO



1 VEZ AO DIA



1 DISPOSITIVO

ELEBRATO

FUROATO DE FLUTICASONA | UMECLIDÍNIO | VILANTEROL | ELLIPTA

ELE RESPIRA

Referências: 1. Van der Palen J et al. NPJ Prim Care Respir Med 2016 26:16079 2. Lipson DA et al. N Engl J Med 2018 378:1671-1680 3. RCM Elebrato Ellipta, fevereiro 2021
DPOC: Doença pulmonar obstrutiva crônica; ICS: Corticosteroide inalado; LABA: Agonista β₂ de longa duração de ação; LAMA: Antagonista muscarínico de longa duração de ação.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM

▼ Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas para <http://www.infarmed.pt/web/infarmed/submissaoram> e para o departamento médico da GlaxoSmithKline para lis.nucleo-farmacovigilancia@gsk.com.

NOME DO MEDICAMENTO Elebrato Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 92 microgramas de furoato de fluticasona, 65 microgramas de brometo de umecidínio equivalente a 55 microgramas de umecidínio e 22 microgramas de vilanterol (como trifenatato). Isto corresponde a um recipiente unidose de 100 microgramas de furoato de fluticasona, 74,2 microgramas de brometo de umecidínio equivalente a 62,5 microgramas de umecidínio e 25 microgramas de vilanterol (como trifenatato). Excipiente com efeito conhecido: cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada. **FORMA FARMACÊUTICA** Pó para inalação em recipiente unidose. **INDICAÇÕES TERAPÊUTICAS** Tratamento de manutenção em doentes adultos com doença pulmonar obstrutiva crónica (DPOC) moderada a grave, que não estejam adequadamente tratados com uma associação de um corticosteroide para inalação e um agonista beta-2 de longa duração de ação ou uma associação de um agonista beta-2 de longa duração de ação e um antagonista muscarínico de longa duração de ação (ver RCM para informação sobre efeitos sobre o controlo dos sintomas e prevenção das exacerbações). **POSOLOGIA E MODO DE ADMINISTRAÇÃO** Adultos A dose máxima recomendada é uma inalação 1x/dia, à mesma hora em cada dia. Doentes idosos, Compromisso renal e Compromisso hepático Não é necessário ajustar a posologia. Utilizar com precaução em doentes com compromisso hepático moderado a grave. População pediátrica A utilização não é relevante na população pediátrica (<18 anos) para a indicação de DPOC. Modo de administração Via inalatória. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram nasofaringite, cefaleia e infeção das vias respiratórias superiores. **Infeções e infestações** Frequentes Pneumonia, infeção das vias respiratórias superiores, bronquite, faringite, rinite, sinusite, gripe, nasofaringite, candidíase da boca e da garganta e infeção do trato urinário Pouco frequentes Infeção viral das vias respiratórias superiores **Doenças do sistema imunitário** Raras Reações de hipersensibilidade, incluindo anafilaxia, angioedema, urticária e erupção cutânea **Doenças do sistema nervoso** Frequentes Cefaleia **Afeções oculares** Desconhecido Visão turva **Cardiopatias** Pouco frequentes Taquiarritmia supraventricular, taquicardia e fibrilhação auricular **Doenças respiratórias, torácicas e do mediastino** Frequentes Tosse e dor orofaríngea Pouco frequentes Disfonia **Doenças gastrointestinais** Frequentes Obstipação Pouco frequentes Boca seca **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia e dor no pescoço Pouco frequentes Fraturas **TITULAR DA AIM** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** fevereiro 2021. **APRESENTAÇÃO:** Elebrato Ellipta 92 mcg+55 mcg+22mcg, 30 doses. **Regime de Participação:** Escalão B. Regime Geral 69%; Regime Especial 84%. Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Medicamento sujeito a receita médica. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial- Portela & C^a, S.A., -A Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. **DMgM_A PT210310**

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