

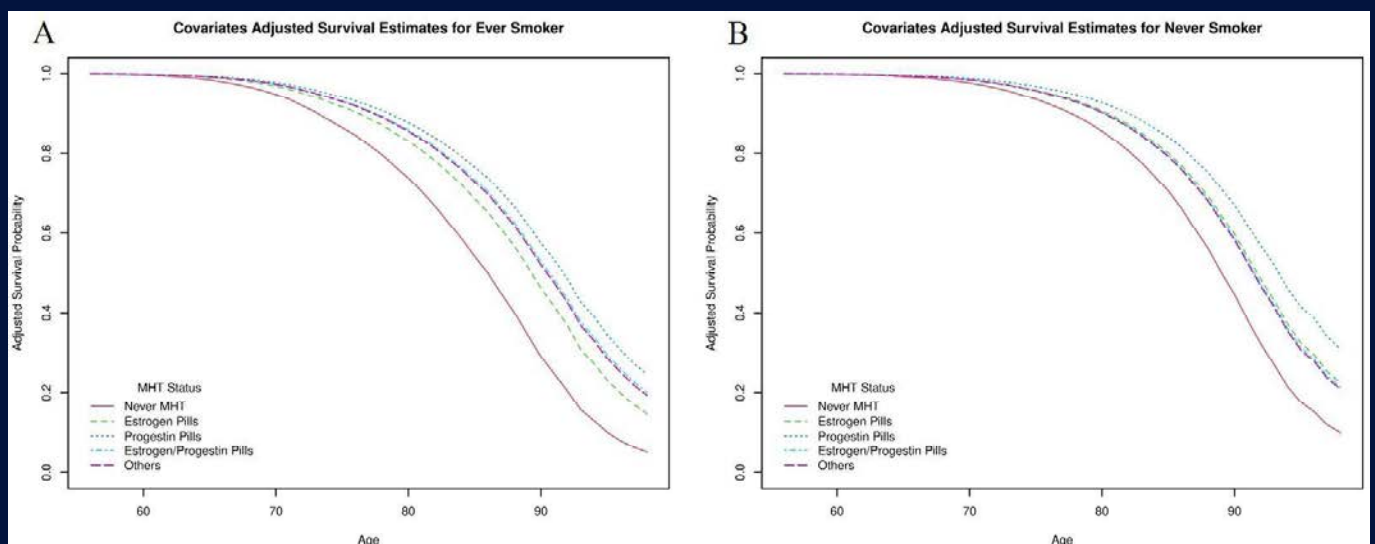
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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Edição Portuguesa





* **Beyfortus® é indicado para a prevenção de doença das vias respiratórias inferiores causada pelo RSV em:**

i) recém-nascidos e lactentes durante a sua primeira época do RSV;

ii) crianças até aos 24 meses de idade que permanecem vulneráveis a doença grave pelo RSV durante a sua segunda época do RSV.¹

Beyfortus® deve ser utilizado de acordo com as recomendações oficiais.¹

Contraindicações: hipersensibilidade à substância ativa ou a qualquer um dos excipientes.¹

** Beyfortus® proporciona pelo menos 5 meses de proteção contra a doença do trato respiratório inferior causada pelo RSV, com base em dados clínicos e farmacocinéticos.¹

† Para lactentes durante a sua primeira época do RSV, a dose recomendada é uma dose única de 50 mg para lactentes com peso corporal <5 kg e uma dose única de 100 mg para lactentes com peso corporal ≥5 kg, administrada por via intramuscular. Para crianças que permanecem vulneráveis a doença grave pelo RSV durante a sua segunda época do RSV, a dose recomendada é uma dose única de 200 mg administrada sob a forma de duas injeções intramusculares (2 x 100 mg). Para crianças submetidas a cirurgia cardíaca com *bypass* cardiopulmonar, pode ser administrada uma dose adicional logo que se verifique estabilização da criança após cirurgia, para garantir níveis séricos adequados de nirsevimab.¹ Consulte o Resumo das

Características do Medicamento para obter informações completas sobre a dosagem nesta circunstância.

‡ Com base nos resultados de dois ensaios multicêntricos aleatorizados, em dupla ocultação e controlados por placebo.³ O *endpoint* primário foi a incidência de ITRI medicamente assistida (incluindo hospitalização), causada por RSV confirmado por RT-PCR. Eficácia demonstrada até 150 dias após a administração.¹⁻³

– **Ensaio de fase 2b:** A população do estudo incluiu 1453 crianças grande prematuras e prematuras moderadas (IG ≥ 29 e < 35 semanas) que entravam na sua primeira época de RSV. As crianças receberam uma dose única intramuscular de 50 mg de Beyfortus® (n=969) ou placebo (n=484). Redução do risco relativo (RRR) em ITRI-RSV MA de 70,1% (IC de 95%: 52,3-81,2; p < 0,001). A incidência foi de 2,6% com

Informações essenciais compatíveis com o Resumo das Características do Medicamento

▼ Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas. Para saber como notificar reações adversas, ver secção “Efeitos Indesejáveis”.

Nome do medicamento Beyfortus 50 mg solução injetável em seringa pré-cheia e Beyfortus 100 mg solução injetável em seringa pré-cheia.

Composição Qualitativa e Quantitativa Cada seringa pré-cheia contém 50 mg de nirsevimab em 0,5 ml (100 mg/ml) e 100 mg de nirsevimab em 1 ml (100 mg/ml), respetivamente. Nirsevimab é um anticorpo monoclonal humano imunoglobulina G1 kappa (IgG1k) produzido em células de ovário de hamster Chinês (CHO) por tecnologia de ADN recombinante. Lista completa de excipientes, ver secção 6.1 do RCM completo. **Forma Farmacêutica** Solução injetável (injetável). Solução transparente a opalescente, incolor a amarela, pH 6,0. **Indicações terapêuticas** Beyfortus é indicado para a prevenção de doença das vias respiratórias inferiores causada pelo Vírus Sincicial Respiratório (VSR), em: i. Recém-nascidos e lactentes durante a sua primeira época do VSR. ii. Crianças até aos 24 meses de idade que permanecem vulneráveis a doença grave pelo VSR durante a sua segunda época do VSR (ver secção 5.1 do RCM completo). Beyfortus deve ser utilizado de acordo com as recomendações oficiais.

Posologia e modo de administração Posologia: *Lactentes durante a sua primeira época do VSR* - A dose recomendada é uma dose única de 50 mg administrados por via intramuscular para lactentes com peso corporal <5 kg e uma dose única de 100 mg administrados por via intramuscular para lactentes com peso corporal ≥5 kg. Beyfortus deve ser administrado desde o nascimento em lactentes nascidos durante a época do VSR. Para outros nascidos fora da época, Beyfortus deve ser administrado idealmente antes da época do VSR. Para outros nascidos fora da época, Beyfortus deve ser administrado idealmente antes da época do VSR. A posologia em lactentes com um peso corporal entre 1,0 kg a <1,6 kg é baseada em extrapolação, não existem dados clínicos disponíveis. Prevê-se que a exposição em lactentes com <1 kg produza exposições mais elevadas do que naqueles que pesam mais. Devem ser considerados cuidadosamente os benefícios e riscos

da utilização de nirsevimab em lactentes <1 kg. Os dados disponíveis em lactentes prematuros extremos (Idade Gestacional [IG] <29 semanas) com menos de 8 semanas de idade, são limitados. Não existem dados clínicos disponíveis em lactentes com idade pós-menstrual (idade gestacional ao nascimento mais idade cronológica) com menos de 32 semanas (ver secção 5.1 do RCM completo). *Crianças que permanecem vulneráveis a doença grave pelo VSR durante a sua segunda época do VSR* - A dose recomendada é uma dose única de 200 mg administrada sob a forma de duas injeções intramusculares (2 x 100 mg). Beyfortus deve ser administrado, idealmente, antes do início da segunda época do VSR. Em indivíduos submetidos a cirurgia cardíaca com *bypass* cardiopulmonar, pode ser administrada uma dose adicional logo que se verifique estabilização do indivíduo após cirurgia, para garantir níveis séricos adequados de nirsevimab. Se estiverem dentro dos 90 dias, após receberem a primeira dose de Beyfortus, a dose adicional durante a primeira época do VSR deve ser de 50 mg ou 100 mg de acordo com o peso corporal, ou de 200 mg durante a segunda época do VSR. Se decorrerem mais de 90 dias desde a primeira dose, a dose adicional pode ser uma dose única de 50 mg independentemente do peso corporal, durante a primeira época do VSR, ou 100 mg durante a segunda época do VSR, para cobrir a época do VSR remanescente. A segurança e eficácia de nirsevimab em crianças com idade compreendida entre os 2 e os 18 anos não foram estabelecidas. Não existem dados disponíveis. **Modo de administração:** Beyfortus é apenas para injeção intramuscular. É administrado por via intramuscular, preferencialmente na zona anterolateral da coxa. O músculo glúteo não deve ser utilizado por rotina como um local de injeção, devido ao risco de lesão no nervo ciático. Se forem necessárias duas injeções, devem ser utilizados locais de injeção diferentes. Para instruções sobre requisitos especiais de manuseamento (ver secção 6.6. do RCM completo).

Contraindicações Hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção 6.1 do RCM completo. **Efeitos indesejáveis** Resumo do perfil de segurança A reação adversa mais frequente foi erupção cutânea (0,7%), que ocorreu dentro de 14 dias após a administração. A maioria dos casos foi de intensidade ligeira a moderada. Adicionalmente, pirexia e reações no local da injeção foram notificadas com uma taxa de 0,5% e 0,3% dentro de 7 dias após a administração, respetivamente. As reações no local da injeção não foram graves.

A Sanofi e a AstraZeneca estão a colaborar no desenvolvimento e comercialização de Beyfortus®.

SANOFI PRODUTOS FARMACÊUTICOS, LDA, Sede Social Empreendimento Lagoas Park, Edifício 7 - 3º Piso, 2740-244 Porto Salvo, Portugal. Capital social: € 26.815.015,00 matriculada na CRC de Cascais, sob o número único de matrícula e identificação de pessoa coletiva 500 134 960, Tel.: +351 21 3589400, email: geral.pt@sanofi.com - www.sanofi.pt

O poder de reduzir o caos na época do RSV

sanofi

Beyfortus® é um anticorpo de ação prolongada e direta **desenvolvido para proteger todos os recém-nascidos e lactentes***, contra a doença do trato respiratório inferior (DTRI) provocada pelo vírus sincicial respiratório (RSV).^{††}

Uma **única dose** reduziu o risco de infecção do trato respiratório inferior por RSV que requer assistência médica (ITRI-RSV MA) vs. placebo em recém-nascidos e lactentes.^{†,§,1-3}

Beyfortus®
(nirsevimab)

DISPONÍVEL
NA ÉPOCA 2024/25 PARA AS
CRIANÇAS ELEGÍVEIS*



Beyfortus® versus 9,5% com placebo.¹² Os tipos e as frequências dos acontecimentos adversos foram semelhantes nos grupos de Beyfortus® e de placebo.²

– **Ensaio MELODY de fase 3:** A população do estudo incluiu 3012 crianças de termo e prematuras tardias (IG ≥ 35 semanas) que entravam na sua primeira época de RSV. As crianças receberam uma dose única intramuscular de 50 mg de Beyfortus®, se peso corporal <5 kg ou 100 mg de Beyfortus® se peso corporal ≥5 kg no momento da administração de Beyfortus® (n=2009), ou de placebo (n=1003). RRR em ITRI por RSV medicamente assistida de 76,4% (IC de 95%: 62,3-85,2). A incidência foi de 1,2% com Beyfortus® versus 5,4% com placebo.¹³ Os tipos e as frequências dos acontecimentos adversos foram semelhantes nos braços de Beyfortus® e placebo.^{3,4}

§ As reações adversas notificadas em crianças que receberam Beyfortus® em ensaios clínicos, foram erupção cutânea, reação no local da injeção e pirexia. A ocorrência foi pouco frequente (≥ 1/1.000 a < 1/100).¹ Consultar o RCM para detalhes completos sobre o perfil de segurança.

IC, intervalo de confiança; **IG**, idade gestacional; **DTRI**, doença do trato respiratório inferior; **ITRI**, infecção do trato respiratório inferior; **MA**, medicamente assistida; **RRR**, redução do risco relativo; **RSV**, vírus sincicial respiratório; **RT-PCR**, reação em cadeia da polimerase via transcriptase reversa.

1. Resumo das Características do Medicamento (RCM) de Beyfortus. Setembro 2024. **2.** Griffin MP et al. N Engl J Med 2020; 383(5): 415-425. **3.** Muller WJ et al. N Engl J Med 2023; 388(16): 1533-1534. **4.** Hammit LL et al. N Engl J Med 2022; 386(9): 837-846.

Lista tabelada de reações adversas A tabela 1 apresenta as reações adversas notificadas em 2966 lactentes de termo e pré-termo (IG ≥29 semanas) que receberam nirsevimab em ensaios clínicos e em contexto pós-comercialização (ver secção 4.4 do RCM completo). As reações adversas notificadas a partir de ensaios clínicos controlados são classificadas por Classe de Sistema de Órgãos (CSO) MedDRA. Dentro de cada CSO, os termos preferenciais são apresentados por frequência decrescente e em seguida por ordem decrescente de gravidade. As frequências de ocorrência de reações adversas são definidas como: muito frequentes (≥1/10); frequentes (≥1/100 a <1/10); pouco frequentes (≥1/1000 a <1/100); raros (≥1/10 000 a <1/1000); muito raros (<1/10 000) e desconhecido (não pode ser calculado a partir dos dados disponíveis). **REAÇÕES ADVERSAS FREQUÊNCIA Doenças do sistema imunitário** Hipersensibilidade^a - Desconhecida **Afeções dos tecidos cutâneos e subcutâneos** Erupção cutânea^b - Pouco frequentes; **Perturbações gerais e alterações no local de administração** Reação no local da injeção^c; Pirexia - Pouco frequentes. ^aReação adversa de notificação espontânea. ^bErupção cutânea foi definida pelos seguintes grupos de termos preferenciais: erupção cutânea, erupção maculopapular, erupção macular. ^cReação no local da injeção foi definida pelos seguintes grupos de termos preferenciais: reação no local da injeção, dor no local da injeção, endurecimento no local da injeção, edema no local da injeção, inchaço no local da injeção. **Lactentes com risco mais elevado de doença grave pelo VSR na sua primeira época** A segurança foi avaliada no MEDLEY em 918 lactentes com risco mais elevado de doença grave por VSR, incluindo 196 lactentes extremamente prematuros (IG <29 semanas) e 306 lactentes com doença pulmonar crónica por prematuridade, ou doença cardíaca congénita hemodinamicamente significativa a entrar na sua primeira época do VSR, que receberam nirsevimab (n=614) ou palivizumab (n=304). O perfil de segurança de nirsevimab em lactentes que receberam nirsevimab na sua primeira época do VSR foi comparável ao comparador palivizumab e consistente com o perfil de segurança de nirsevimab em lactentes de termo e pré-termo com IG ≥29 semanas (D5290C00003 e MELODY). **Lactentes que permanecem vulneráveis a doença grave pelo VSR na sua segunda época** A segurança foi avaliada no MEDLEY em 220 crianças com doença pulmonar crónica da prematuridade ou com doença cardíaca congénita hemodinamicamente significativa que receberam nirsevimab

ou palivizumab na primeira época do VSR e que continuaram a receber nirsevimab na sua segunda época do VSR (180 participantes receberam nirsevimab nas épocas 1 e 2; 40 receberam palivizumab na época 1 e nirsevimab na época 2). O perfil de segurança de nirsevimab em crianças que receberam nirsevimab na sua segunda época do VSR foi consistente com o perfil de segurança de nirsevimab em lactentes de termo e pré-termo com IG ≥29 semanas (D5290C00003 e MELODY). A segurança foi também avaliada no MUSIC, um ensaio em regime aberto, não controlado, de dose única em 100 lactentes e crianças imunocomprometidos com ≤24 meses, que receberam nirsevimab na sua primeira ou segunda época do VSR. Isto incluiu participantes com pelo menos uma das seguintes condições: imunodeficiência (combinada, anticorpos ou outra etiologia) (n=33); corticoterapia sistémica de dose elevada (n=29); transplante de órgão ou de medula óssea (n=16); a receber quimioterapia imunossupressora (n=20); outra terapia imunossupressora (n=15) e infecção por VIH (n=8). O perfil de segurança de nirsevimab foi consistente com o esperado para uma população de crianças imunocomprometidas e com o perfil de segurança de nirsevimab em lactentes de termo e pré-termo com IG ≥29 semanas (D5290C00003 e MELODY). O perfil de segurança de nirsevimab em crianças durante a sua segunda época do VSR foi consistente com o perfil de segurança de nirsevimab observado durante a sua primeira época do VSR. Notificação de suspeitas de reações adversas A notificação de suspeitas de reações adversas após a autorização do medicamento é importante, uma vez que permite uma monitorização contínua da relação benefício-risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas diretamente ao INFARMED, I.P.: Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos, Parque da Saúde de Lisboa, Av. Brasil 53, 1749-004 Lisboa, Tel: +351 21 798 73 73 Linha do Medicamento: 800222444 (gratuita) E-mail: farmacovigilancia@infarmed.pt **Data de revisão do texto:** setembro 2024. Medicamento sujeito a receita médica. Para mais informações, contactar o Representante Local do Titular da Autorização de Introdução no Mercado.

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Editorial

Estamos a chegar ao fim de mais um ano que foi rico em produção científica de qualidade, pelo que estamos de volta com mais uma edição com uma seleção de artigos das revistas *Thorax* e *Archives of Disease in Childhood*, chamando a sua atenção para alguns deles.

O presente número da Revista apresenta vários artigos de grande interesse sobre doença respiratória pediátrica, mas optamos por realçar os dois primeiros: o artigo “Custos diretos e indiretos da asma pediátrica no Reino Unido” que mostra como a asma pediátrica representa um encargo económico significativo para o serviço de saúde, para as famílias e para a sociedade e como os esforços para melhorar o controlo da asma podem gerar reduções de custos significativas. Por sua vez, o artigo “A humidade visível no quarto de uma criança está associada a um aumento da morbilidade respiratória no início de vida”, nas suas conclusões, recomenda que, em crianças que apresentam sintomas respiratórios recorrentes, os médicos investiguem a existência e a localização da humidade, cuja presença pode ajudar a definir as prioridades das famílias que necessitam de uma avaliação urgente da humidade doméstica e de obras de reparação.

No artigo seguinte “Impacto indireto da vacina pneumocócica conjugada 13-valente infantil (VPC13) em idosos canadianos”, os autores recolheram casos mensais de DPI e pneumonia por todas as causas de bases de dados de laboratórios e de administrações de saúde entre janeiro de 2005 e dezembro de 2018 e concluíram que as taxas de todas as DPI ou DPI específicas do serotipo da VPC para adultos mais velhos em Ontário e na British Columbia não se alteraram nos 8 anos após a implementação do programa infantil da VPC13 e concluem que a proteção comunitária indireta dos adultos mais velhos contra a hospitalização por doença pneumocócica estagnou apesar da maturação dos programas de vacinação infantil VPC13 nas duas províncias canadianas.

No artigo seguinte “A menopausa precoce e a terapia hormonal como fatores determinantes dos resultados de saúde pulmonar”, procurou-se avaliar as associações de menopausa precoce e terapia hormonal menopáusica (THM) com morbilidades e mortalidades pulmonares, utilizando dados do estudo prospetivo *Prostate, Lung, Colorectal and Ovarian* (PLCO). Entre as principais conclusões, salienta-se que as fumadoras com menopausa precoce devem ser assinaladas para a cessação tabágica e rastreio de cancro do pulmão (CP), independentemente do tipo de menopausa e que as utilizadoras de THM apresentaram uma menor probabilidade de morrer devido a CP e de doenças respiratórias em ex-fumadoras.

Por fim, referimos um artigo importante na área da Doença pulmonar ocupacional: “Relação entre a exposição cumulativa à sílica e a silicose” trata-se de uma revisão sistemática e uma meta-análise dose-resposta”. A principal conclusão dos autores é que apesar da heterogeneidade significativa, os resultados apoiam uma redução dos limites de exposição admissíveis de 0,1 mg/m³, para 0,05 mg/m³, particularmente entre as populações mineiras, sendo necessária mais investigação entre as populações não mineiras, uma vez que apenas dois estudos foram elegíveis.

Uma vez que se aproxima a época de festas, desejamos a todos que desfrutem deste período para convívio e reencontro com familiares e amigos e desejamos um excelente ano de 2025.

Jaime Correia de Sousa

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Exposições pré-natais a tabaco e a combustíveis de biomassa ou fósseis e pieira no início da infância na África do Sul

Rachel Nadif

A asma é a doença crônica mais prevalente na infância. Com base no estudo *Global Burden of Diseases, Injuries and Risk Factors*, os casos de incidência global de asma em crianças aumentaram 7,07% entre 1990 e 2019, sendo a maior incidência observada em crianças com menos de 5 anos.¹ Nestas crianças mais novas, a asma é difícil de diagnosticar, definindo-se frequentemente por episódios de pieira caracterizados pela sua data de início (início ou final da infância) e/ou pela sua duração (transitória ou persistente).² Estudos epidemiológicos em diferentes populações revelaram o papel fundamental dos fatores ambientais na influência da evolução da pieira no início de vida para a asma, incluindo a predisposição genética, os vírus, a sensibilidade alérgica, a exposição precoce ao fumo do tabaco e a interação com o microbioma.³ Reconhece-se agora que a exposição a uma má qualidade do ar exterior e interior afeta a saúde respiratória ao longo da vida, a partir do período pré-natal, e as crianças que vivem em países de baixos e médios rendimentos (PBM) enfrentam maiores desafios em termos de qualidade do ar, particularmente devido a outras fontes de poluição interior, incluindo o aumento da dependência de combustíveis sólidos, fogueiras e a rápida urbanização.⁴ É essencial uma melhor compreensão das associações entre os fatores ambientais, particularmente aqueles que são evitáveis, e a persistência da pieira para a prevenção e gestão da asma.

Até à data, são escassos os resultados de estudos epidemiológicos longitudinais sobre a exposição pré-natal a fatores ambientais e a pieira no início da infância, em particular nos PBM. Devemos mencionar o estudo de Vanker *et al*, que investigou longitudinalmente a exposição pré-natal e pós-natal a tolueno, benzeno, partículas com diâmetro inferior a 10 µm (PM₁₀) e fumo do tabaco no ambiente (FTA), utilizando medições objetivas que muitas vezes não foram efetuadas em estudos anteriores, e as suas associações com a pieira num estudo de coorte de nascimentos na África do Sul.⁵ O estudo incluiu 1137 mães com 1143 nados-vivos e concluiu que o tabagismo materno pré-natal e pós-natal estava associado à pieira (taxa de incidência de 2,09 (IC 95% 1,54 a 2,84) e 1,27 (1,03 a 1,56), respetivamente). Infelizmente, não foram investigados quais-

quer poluentes do ar exterior. A qualidade do ar interior e exterior em relação à pieira foi muito bem explorada em edição da Thorax por Asharam *et al* Ema Mother and Child in the Environment Birth Cohort.⁶ Utilizando uma análise de tempo-até-evento, foram investigadas as associações em 520 pares mãe-filho de Durban, África do Sul. Os autores levantaram a hipótese de que a exposição pré-natal a dióxido de azoto (NO₂) e PM_{2.5} no exterior, bolor e humidade no interior, biomassa e combustível, bem como a exposição a FTA em casa e no trabalho, podem estar associadas a pieira recorrente no início da infância, resultando num diagnóstico mais precoce deste resultado. As mães foram entrevistadas no recrutamento e a cada trimestre da gravidez. Foram registados dados sobre a idade, saúde geral e história reprodutiva, educação, rendimentos, residência, tipo de habitação, antecedentes de alcoolismo e tabagismo da mãe. As crianças foram acompanhadas desde o nascimento até aos 48 meses. Foi aplicado um modelo de regressão híbrido e de dispersão/ utilização do solo para a previsão da poluição atmosférica para estimar a exposição ambiental média anual na morada de cada mãe, e ajustado para uma estimativa durante o primeiro trimestre da gravidez e o mês de nascimento. Entre as 520 crianças que compareceram a pelo menos uma consulta clínica, 85% foram seguidas aos 6 meses, 76% aos 12 meses, 49% aos 24 meses, 29% aos 36 meses e 22% aos 48 meses. A pieira única e recorrente foi registada em 16% e 11% dos participantes na consulta, respetivamente. A análise do tempo até ao evento mostrou um tempo significativamente mais curto para a ocorrência de pieira única e recorrente nas crianças de mães expostas ao FTA pré-natal, em comparação com as não expostas, e um tempo significativamente mais curto para a ocorrência de pieira recorrente nas crianças cujos agregados familiares utilizavam biomassa ou combustíveis fósseis, em comparação com os agregados familiares que utilizavam fontes elétricas. As crianças de mães expostas ao FTA pré-natal apresentaram um risco mais elevado de pieira única e recorrente (HR ajustado(a) 1,69 (IC 95% 1,1 a 2,6) e HRa 3,76 (1,3 a 10,6), respetivamente) em comparação com as não expostas. As crianças cujo agregado familiar utilizava biomassa ou combustíveis fósseis apresentaram um risco superior não significativo de pieira recorrente (HRa 3,09 (0,91 a 10,45)) em comparação com os agregados familiares que utilizavam fontes elétricas. Estes resultados fornecem mais evidências da associação entre a exposição pré-natal

a poluentes de risco e a pieira, destacando a exposição à biomassa e aos combustíveis e confirmando o fumo do tabaco. Ao contrário dos poucos estudos anteriores neste domínio, nem a pieira única nem a pieira recorrente foram significativamente associadas à exposição a NO₂ ou PM_{2.5}. Como os autores sugerem, a sua escolha de se concentrar na exposição pré-natal pode ter resultado numa perda dos efeitos dos poluentes do ar exterior nos meses após o nascimento, e os riscos mais elevados que observaram no primeiro mês de nascimento em comparação com o primeiro trimestre de gravidez parecem confirmar esta hipótese. Também podemos presumir que as mães passaram mais tempo em casa do que no exterior durante a gravidez, uma informação que teria sido importante recolher. A taxa de perda de seguimento foi superior a 50% após 12 meses, mas a análise do tempo até ao evento, realizada pela primeira vez em África no âmbito deste estudo, permitiu o tratamento de todos os dados disponíveis.

Seis fatores de risco ambiental foram estudados por Asharam *et al*,⁶ mas muitos mais precisam de ser investigados. De facto, o projeto Human Early-Life Exposome examinou as associações de 53 fatores ambientais pré-natais e 105 fatores ambientais na infância com a saúde cardiometabólica, respiratória/alérgica e mental em 870 crianças (com idades compreendidas entre os 6 e os 12 anos) de seis coortes de nascimento europeias.⁷ O estudo confirmou o papel do tabaco e dos poluentes atmosféricos e identificou novos fatores, como os animais de estimação e os espaços azuis, que merecem uma investigação mais aprofundada. Não há dúvida de que o estudo *Cohort for Childhood Origin of Asthma and allergic diseases* (COCOA), uma coorte de pares mãe-filho representativa de uma população coreana do centro da cidade, irá fornecer novos dados nesta área.⁸ Através da integração de dados de sequências multiômicas e de informações sobre o exposoma, o estudo COCOA também pretende fornecer dados aprofundados sobre as vias fisiopatológicas envolvidas na dermatite atópica, alergia alimentar, rinite alérgica e asma. Atendendo ao facto de as mães e as crianças passarem provavelmente a maior parte do seu tempo em ambientes fechados, onde as concentrações de poluentes específicos são geralmente 2 a 5 vezes mais elevadas do que no exterior, a literatura recente justifica a preocupação com a exposição pré-natal e precoce a fatores ambientais. Como algumas destas exposições podem ser evitadas, é altura de tomar medidas eficazes para preservar a saúde das futuras gerações em todo o mundo.

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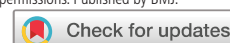
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Referências: 1. Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento], AstraZeneca AB, SE-151 85 Södertälje Suécia; outubro 2023. Acedido em www.infarmed.pt em novembro 2023. 2. Bevespi Aerosphere 5 microgramas/7,2 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento], AstraZeneca AB, SE-151 85 Södertälje Suécia; setembro 2023. Acedido em www.infarmed.pt em novembro 2023. 3. Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ. In-Hospital and One-Year Mortality and Their Predictors in Patients Hospitalized for First-Ever Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Population-Based Study. *Bai C, editor. PLoS ONE*. 2014 Dec 9;9(12):e114866.

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Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada, a dose que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrónio, equivalente a 7,2 microgramas de glicopirrónio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada (isto é, a dose que sai da válvula) de 10,4 microgramas de brometo de glicopirrónio, equivalente a 8,3 microgramas de glicopirrónio, e 5,8 microgramas de fumarato de formoterol di-hidratado. **Indicações terapêuticas:** Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crónica (DPOC). **Bevespi Aerosphere** pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasma paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se ocorrer broncospasma paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tireotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocalcemia:** Os agonistas β_2 -adrenérgicos podem causar hipocalcemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocalcemia pode ser potenciada por hipoxia e tratamento concomitante. **Hiperglicemia:** A inalação de doses elevadas de agonistas β_2 -adrenérgicos pode provocar o aumento da glucose plasmática. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. **Doentes com compromisso renal grave:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. Doentes com compromisso hepático grave: Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2 -adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2 -adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β_2 -adrenérgicos de curta duração de ação, metilxantinas e esteroides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteroides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico inicial dos agonistas β_2 -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores β -adrenérgicos:** Os bloqueadores β -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β -adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β -adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. **Outras interações farmacodinâmicas:** Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. **Amamentação:**

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

Informações essenciais compatíveis com o Resumo das Características do Medicamento

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

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ARTIGO ORIGINAL

Eficácia da imunoprofilaxia com nirsevimab face aos resultados relacionados com o vírus sincicial respiratório em contexto hospitalar e de cuidados primários: um estudo de coorte retrospectivo em crianças na Catalunha (Espanha)

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RESUMO

Contexto Na Catalunha, crianças com menos de 6 meses de idade foram elegíveis para receber nirsevimab, um novo anticorpo monoclonal contra o vírus sincicial respiratório (VSR). O nosso objetivo foi analisar a eficácia de nirsevimab em relação aos resultados dos cuidados primários e hospitalares.

Métodos Estudo de coorte retrospectivo entre 1 de outubro de 2023 e 31 de janeiro de 2024, incluindo todos as crianças nascidas entre abril e setembro de 2023. Estabelecemos duas coortes com base na administração de nirsevimab (imunizados e não imunizados). Acompanhámos os indivíduos até ao momento mais próximo de um resultado - infecção por VSR, bronquiolite e pneumonia atendidas em cuidados primários, visitas de emergência hospitalar devido a bronquiolite, admissão hospitalar ou admissão na unidade de cuidados intensivos (UCI) devido a bronquiolite por VSR - morte ou fim do estudo. Utilizámos a estimativa de Kaplan-Meier e ajustámos modelos de regressão de Cox utilizando uma escala temporal no calendário para estimar os HR e os respectivos IC de 95%.

Resultados Entre 26 525 crianças, uma dose de nirsevimab conduziu a um HR ajustado para admissão hospitalar devido a bronquiolite por VSR de 0,124 (IC 95%: 0,086 a 0,179) e a um HR ajustado para admissão na UCI de 0,099 (IC 95%: 0,041 a 0,237). Adicionalmente, os HR ajustados observados para visitas de emergência foram de 0,446 (IC 95%: 0,385 a 0,516) e 0,393 (IC 95%: 0,203 a 0,758) para pneumonia viral, 0,519 (IC 95%: 0,467 a 0,576) para bronquiolite atendida em cuidados primários e 0,311 (IC 95%: 0,200 a 0,483) para infecção por VSR.

Conclusão Demonstrámos a eficácia de nirsevimab com reduções de 87,6% e 90,1% nas admissões hospitalares e na UCI, respetivamente. Estes resultados oferecem uma orientação crucial para as autoridades de saúde pública na implementação de campanhas de imunização contra o VSR.

INTRODUCTION

Respiratory syncytial virus (RSV) infection is a worldwide public health concern due to its high contagiousness and potential to cause severe illness in the paediatric population.¹ It is estimated that RSV is responsible for 70% of all bronchiolitis and 25% of pneumonia in infants under 1 year of age.² RSV infection typically exhibits a seasonal pattern, with peak incidence in Spain usually observed between October and March.³

In March 2023, nirsevimab was commercialised in Spain. This recombinant human IgG1 kappa monoclonal antibody has demonstrated its efficacy

Key messages

What is the key question?

- Respiratory syncytial virus (RSV) is a main cause of lower respiratory tract infections, such as pneumonia and bronchiolitis, in infants.
- Nirsevimab, a new monoclonal antibody, has demonstrated high efficacy in preventing RSV-associated disease, particularly in reducing hospitalisation, as shown in previous clinical trials.

What is the bottom line?

- Catalonia initiated an RSV immunisation campaign, presenting a unique opportunity to assess the effectiveness of nirsevimab against various outcomes.
- Our study reveals substantial effectiveness, with an 87.6% reduction in hospital admissions and a 90.1% reduction in intensive care unit admissions due to RSV bronchiolitis.
- Additionally, we observed notable reductions in less severe outcomes, including primary care-diagnosed bronchiolitis (48.1%), RSV infections (68.9%), viral pneumonia (60.7%) and hospital emergency visits for bronchiolitis (55.4%).

Why read on?

- These findings offer timely and crucial insights for healthcare authorities, informing strategies for RSV prevention and the planning of immunisation campaigns.

and safety in preventing RSV infections in infants during their first epidemic season.^{4–9}

Catalonia, an 8-million-inhabitant autonomous community in the northeast of Spain, introduced the recommendation and financing of nirsevimab in October 2023 as part of the infant immunisation programme.¹⁰ All infants born between April and September 2023 were offered a dose of nirsevimab in primary care practices (PCPs) during October, in addition to all newborns born between October 2023 and March 2024, preferably in public and private hospitals, or in PCPs during the first days of life. At the time of writing, the RSV epidemic wave

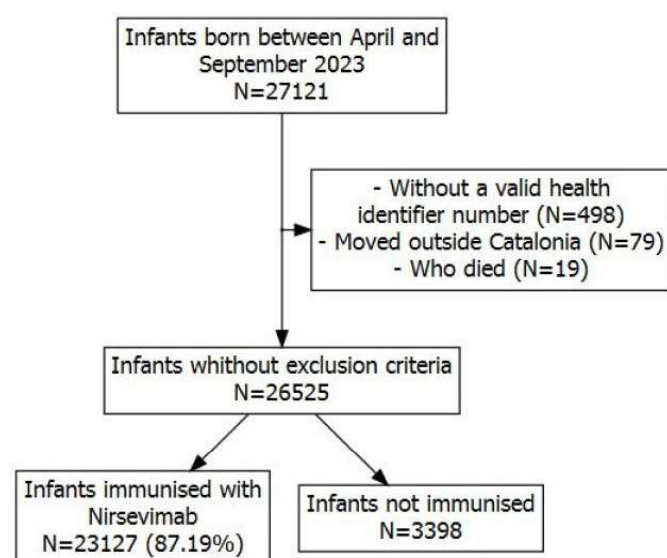


Figure 1 Population flow chart.

has already ended (online supplemental figure 1), but the nirsevimab campaign is still underway for children born after October. Since the number of children is large and the observation period is adequate, it is a good time to analyse the data, focusing on the first group of children and providing useful and timely information to plan next season. The objective of the study is to assess nirsevimab's effectiveness in infants born between April and September 2023 during their first epidemic season.

METHODS

Study design and settings

We conducted a retrospective cohort study using routinely collected data from five Catalan health databases. Nirsevimab exposure was obtained from the Catalan Shared Clinical Records, a comprehensive clinical database of electronic medical records that integrates data from the entire Catalan health system. We further linked data to the primary care electronic health records (EHRs) to analyse primary care-related outcomes. Data on hospital and intensive care unit (ICU) admissions were obtained from the Minimum Basic Data Set (CMBD in Catalan) and hospital emergency department visits from the CMBD-UR. Covariables and the eligible population were sourced from the central population register of the Catalan health service.¹¹

All public PCPs in Catalonia use the same EHR system, known as ECAP, which has been previously validated and used for epidemiological research.¹² The CMBD furnishes information on hospi-

tal discharges from all hospitals in Catalonia, encompassing both public and private hospitals.¹³

Participants and follow-up

We included all infants born between April and September 2023 in Catalonia and deemed eligible for immunisation with nirsevimab. We excluded those without a valid health identifier number and those who died or moved outside Catalonia before the start of the immunisation campaign. For the analysis of the primary care-related outcomes, we also excluded those infants who were not assigned to one of the public PCPs in Catalonia contributing to our database.

The study was conducted from 1 October 2023 to 31 January 2024. By the end of this period, the RSV epidemic in Catalonia had already concluded (online supplemental figure 1A,B). Two cohorts were established based on the nirsevimab administration date:

- Exposed cohort (immunised with nirsevimab): infants who received a dose of nirsevimab during the study period.
- Control cohort (non-immunised): infants who did not receive any dose of nirsevimab during the study period.

Exposure was dynamically defined. This means that infants who received one dose of nirsevimab may have previously contributed to the control cohort until the date of administration, at which point they became part of the exposed cohort.

We followed non-immunised participants from the beginning of the immunisation campaign in Catalonia (1 October 2023) until the earliest of receiving a dose of nirsevimab (at which point they switched to the exposed cohort), an outcome, death or the end of the study. Immunised participants were followed from the day they received nirsevimab immunoprophylaxis until the earliest of an outcome, death or the end of the study.

STUDY OUTCOMES

Several outcomes were analysed:

- Primary care attended bronchiolitis: defined as a clinical diagnosis of bronchiolitis based on International Classification of Diseases 10th version (ICD-10) codes recorded in the primary care EHR (online supplemental table 1).
- RSV infection: measured as a positive rapid antigen test performed in primary care settings. Since 2021, rapid antigen tests for influenza (A and B), adenovirus, SARS-CoV-2 and RSV have been available in all paediatric PCPs for testing children with respiratory infection symptoms or fever without a focus.¹⁴
- Viral pneumonia diagnosed in primary care: viral pneumonia diagnoses recorded in the primary care EHR were defined according to the ICD-10 classification, including all codes used in the Information System for Surveillance of Infections in Catalonia (online supplemental table 1).¹⁵
- Hospital emergency department visits due to bronchiolitis: any hospital emergency visit for all-cause bronchiolitis.
- Hospital admission for RSV-related disease: hospital admission with a discharge diagnosis of bronchiolitis due to RSV. In Catalonia, all paediatric patients with suspected acute low respiratory tract infections (LRTIs) who are admitted to hospital are tested for RSV as well as influenza A and B viruses and SARS-CoV-2.
- Admission to ICU for RSV-related disease: any admission to the ICU during the hospital stay due to bronchiolitis caused by RSV. In our analysis, hospital emergency department visits and primary care diagnoses outcomes encompassed all-cause bronchiolitis, as the majority of cases are reported as non-specific bronchiolitis (96.2% in primary care attended bronchiolitis and 87.4% in emergency visits).

Furthermore, we analysed the occurrence of a negative control outcome, (impetigo diagnoses registered in the primary care EHR), to identify potential unmeasured confounding. Negative control outcomes are events that are known not to be causally affected by the exposure of interest, here nirsevimab immunisation.¹⁶

Finally, we conducted a sensitivity analysis including hospital admissions for bronchiolitis caused by other pathogens as an outcome, for which no association with nirsevimab was expected.

Table 1 Baseline characteristic stratified by immunisation status

Variable	Control group (N=3398)	Nirsevimab group (N=23 127)
Median (IQR) age, days	106 (52–151)	88 (44–134)
Month of birth		
April	803 (23.6%)	1473 (15%)
May	620 (18.2%)	3687 (15.9%)
June	468 (14%)	3804 (16.4%)
July	505 (14.9%)	4055 (17.5%)
August	462 (13.6%)	4042 (17.5%)
September	532 (15.7%)	4066 (17.6%)
Median (IQR) age at the time of immunisation, days	–	106 (63–152)
Male sex	1739 (51.2%)	11 916 (51.5%)
Nationality (Spanish)	2793 (82.2%)	20 154 (87.1%)
Rural	875 (25.8%)	5420 (23.4%)
Median (IQR) Composite socioeconomic index (ISC)	45.2 (32.6–55.6)	43.9 (30.6–54.4)

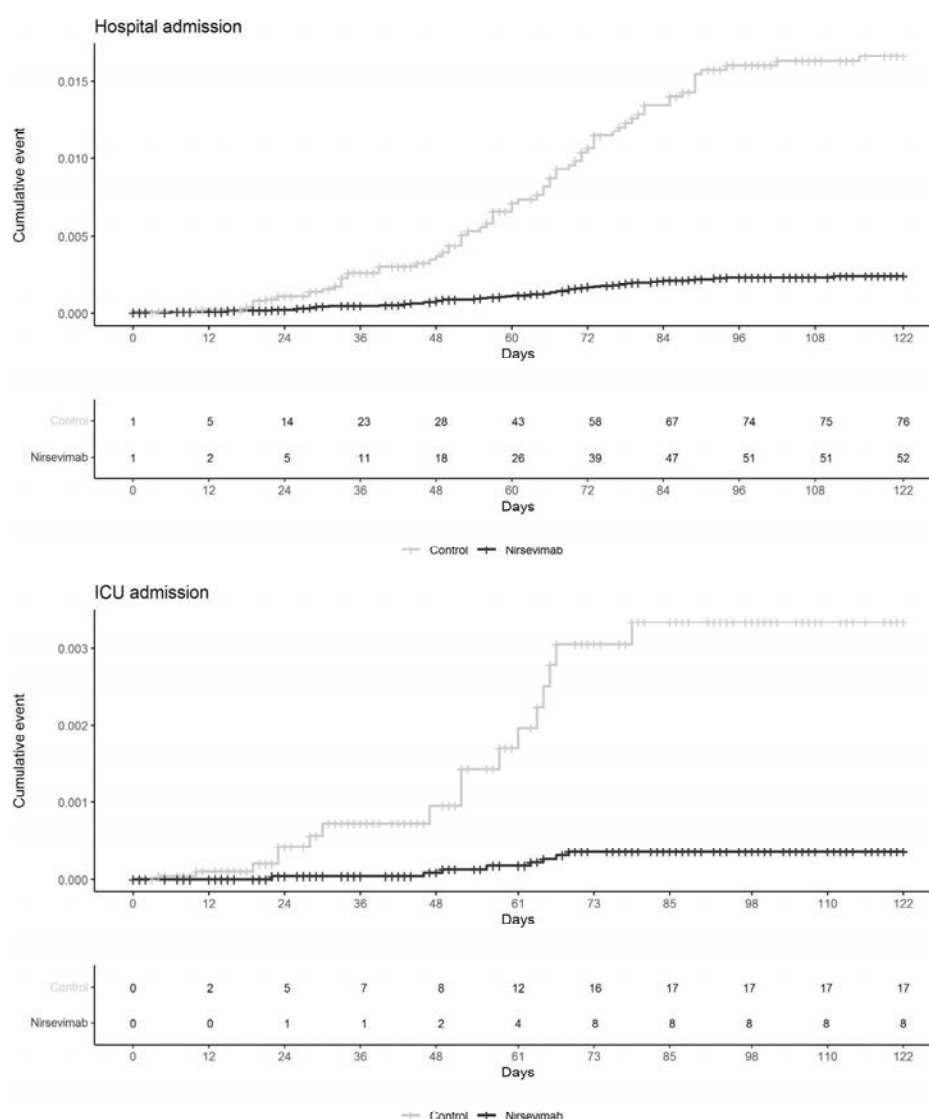


Figure 2 Estimated risk of hospital and intensive care unit (ICU) admissions due to bronchiolitis caused by respiratory syncytial virus according to immunisation status.

Additional covariables

Covariables used for confounding assessment included socio-demographics: age (in days) at the beginning of the study, sex, area of residence, nationality (Spanish or immigrant), rurality and socioeconomic status. We assessed socioeconomic status using the validated socioeconomic index from the Catalan Agency for Healthcare Quality and Assessment, calculated at the health basic area level.¹⁷ Rurality of residence was measured, with rural areas defined by a population <10 000 inhabitants and a density <150 inhabitants per km², as per regional guidance.

Statistical analysis

For descriptive analyses, we expressed continuous variables as median (IQR), and summarised categorical variables as a number (percentages). We assessed confounding by indication by using the standardised mean difference (SMD) of all covariables to compare both cohorts. We considered SMD >0.1 to be imbalanced and adjusted it in multivariable analysis.¹⁸

We computed the cumulative incidence (risk) curves of each outcome using the Kaplan-Meier estimator. Cox regression models using a calendar time scale¹⁹ were then fitted to calculate HRs and 95% CIs for each of the study outcomes according to immunisation status. All Cox models were also adjusted for any confounders with an SMD >0.1. Six models were conducted separately for each of the outcomes. Visual inspection of Schoenfeld residuals against the transformed time was used to evaluate the proportionality of

hazards (online supplemental figure 2). We estimated effectiveness as the per cent reduction in risk (1 minus adjusted HR expressed as percentage). Finally, Cox regression models stratified by month of birth were performed as part of a post hoc analysis requested by one of the manuscript reviewers.

All analyses were conducted using R V.4.0.0 (libraries survival and survminer).^{20,21}

RESULTS

Before exclusions, 27 121 infants born between April and September 2023 were eligible for nirsevimab immunisation. We excluded 596 infants due to exclusion criteria (figure 1). We therefore analysed data from 26 525 infants (97.8%). For the analysis of the primary care outcomes, we excluded 1570 infants (5.9%) not assigned to a public PCP.

By the end of the study period, 23 127 infants (87.2%) had been immunised against RSV. Online supplemental figure 3 shows the rapid uptake of the nirsevimab coverage, with 76.3% of infants having received nirsevimab within the first month of the immunisation campaign.

The control and nirsevimab groups were balanced without adjustment in terms of sex, rurality and socioeconomic status, but differed in age (106 vs 88 days) and nationality (82.2% vs 87.1% of Spanish nationality), all with SMD >0.1 (table 1 and online supplemental figure 4).

Among infants immunised with nirsevimab, 1560 primary care attended bronchiolitis, 604 hospital emergency visits for bronchi-

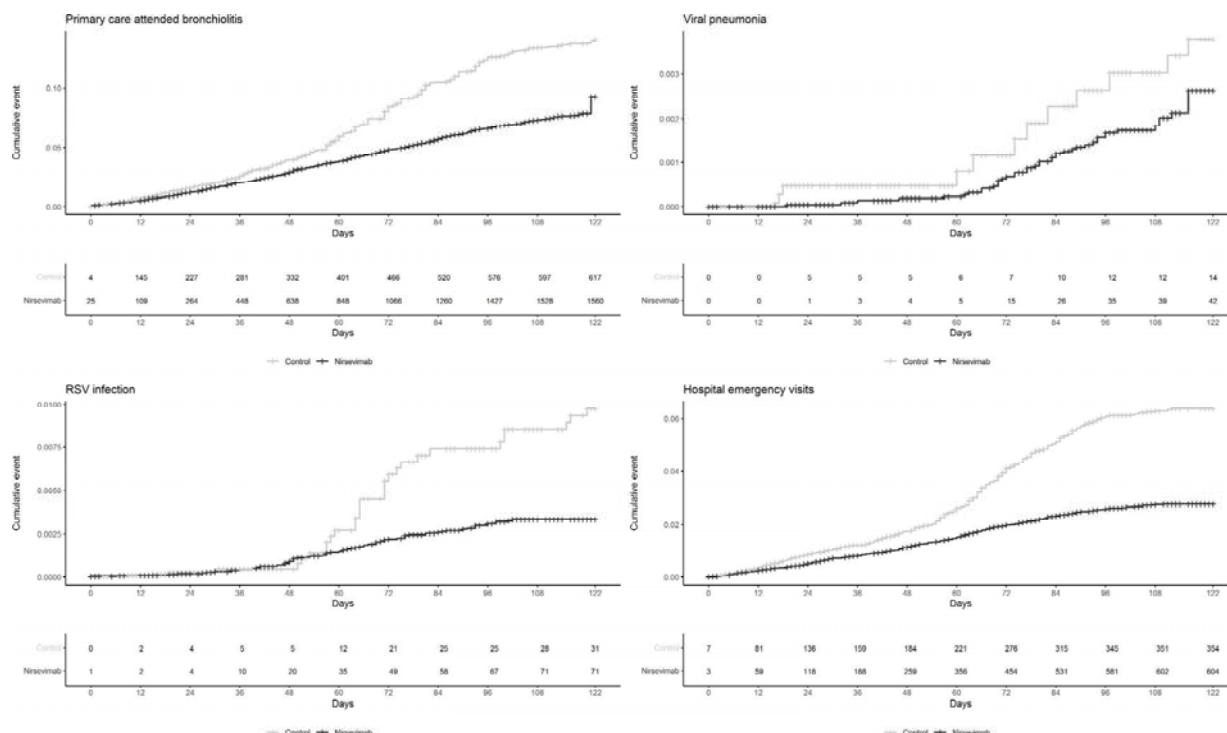


Figure 3 Estimated risk of RSV infections, primary care attended bronchiolitis, viral pneumonia and hospital emergency visits according to immunisation status. RSV, respiratory syncytial virus.

olitis, and 52 hospital admissions and 8 ICU admissions due to RSV bronchiolitis occurred. Conversely, in the control group, we observed 617 primary care bronchiolitis, 354 hospital emergency visits, 76 hospital admissions and 17 ICU admissions. Figures 2 and 3 depict the cumulative incidence of each outcome in both groups. Notably, the control group showed higher incidence rates for all outcomes, particularly for severe cases. For instance, the incidence rates of hospital admission due to RSV bronchiolitis were 9.55 per 100 000 person-days for non-immunised infants, as compared with 2.16 for immunised infants. Similarly, incidence rates of ICU admissions were 2.13 and 0.33, and incidence rates of primary care bronchiolitis were 93.9 and 69.7, respectively (table 2).

A dose of nirsevimab led to an adjusted HR for hospital admission of 0.124 (95% CI: 0.086 to 0.179) and an adjusted HR for ICU admission of 0.099 (95% CI: 0.041 to 0.237). In addition, the adjusted HRs observed for emergency visits were 0.446 (95% CI: 0.385 to 0.516) and 0.393 (95% CI: 0.203 to 0.758) for viral pneumonia, 0.519 (95% CI: 0.467 to 0.576) for primary care bronchiolitis and 0.311 (95% CI: 0.200 to 0.483) for RSV infection (table 2). Table 2 also presents nirsevimab's effectiveness for each outcome, showcasing an effectiveness of 90.1% (95% CI: 76.3% to 95.9%) against ICU admission and 87.6% (95% CI: 82.1% to 91.4%) against hospital admission.

Impetigo diagnoses were used as a negative control outcome. They were recorded at similar frequencies in the two groups leading to an adjusted HR of 1.09 (95% CI: 0.80 to 1.48) (online supplemental figure 5). In addition, in a sensitivity analysis, we estimated

the effectiveness of nirsevimab in preventing hospital admissions due to bronchiolitis caused by other pathogens, with an adjusted HR of 0.936 (95% CI: 0.420 to 2.087), indicating no association. Furthermore, HRs for hospital admission stratified by month (post hoc analysis) were consistent with the main results (online supplemental table 2).

Finally, two deaths were observed in our study population (both not immunised). These deaths were not related to RSV infection but were infants who were admitted to the hospital immediately after birth and remained hospitalised until the date of their death.

DISCUSSION

This study offers a valuable estimation of nirsevimab effectiveness against various outcomes in infants aged <6 months old prior to the onset of their first RSV epidemic season. Using a comprehensive linked database that integrates primary and hospital care data, we investigated the impact of the Catalan immunisation programme on reducing RSV-related outcomes.¹⁰ Our analysis found that nirsevimab effectiveness against hospital and ICU admissions was 87.6% and 90.1%, respectively. Furthermore, we observed significant and clinically relevant reductions in less severe outcomes, including all-cause bronchiolitis attended in primary care (48.1%), RSV infections (68.9%), viral pneumonia (60.7%) and hospital emergency visits due to non-specific bronchiolitis (55.4%). To our knowledge, this study represents the first report to include outcomes of different severity in a real-world setting, providing a

Table 2 Number of different outcomes, incidence rates (per 100 000 person-days), unadjusted HRs, adjusted HRs and effectiveness according to nirsevimab immunisation status

Outcome	Control group		Nirsevimab group		Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Effectiveness (95% CI)
	n	Rate per 100 000 person-days	n	Rate per 100 000 person-days			
RSV infection	31	4.57	71	3.04	0.323 (0.208 to 0.500)	0.311 (0.200 to 0.483)	68.9% (51.7% to 80%)
Primary care attended bronchiolitis	617	93.9	1560	69.7	0.11 (0.461 to 0.568)	0.519 (0.467 to 0.576)	48.1% (42.4% to 53.3%)
Viral pneumonia	14	2.06	42	1.79	0.359 (0.186 to 0.691)	0.393 (0.203 to 0.758)	60.7% (24.2% to 79.7%)
Hospital emergency visits	354	45.1	604	25.5	0.450 (0.389 to 0.520)	0.446 (0.385 to 0.516)	55.4% (48.4% to 61.5%)
Hospital admission	76	9.55	52	2.16	0.133 (0.092 to 0.191)	0.124 (0.086 to 0.179)	87.6% (82.1% to 91.4%)
ICU admission	17	2.13	8	0.33	0.109 (0.045 to 0.260)	0.099 (0.041 to 0.237)	90.1% (76.3% to 95.9%)

ICU, intensive care unit; RSV, respiratory syncytial virus.

comprehensive assessment of the impact of nirsevimab across all levels of care.

Sensitivity analysis showing lack of protection in hospital admissions due to bronchiolitis caused by other pathogens, along with the absence of association between nirsevimab immunisation and our negative control outcome, underscore the robustness of our findings. These results rule out residual confounding in our cohorts.¹⁶

The observed differences in effectiveness between RSV infections and bronchiolitis diagnosed in primary care may be attributed to the fact that within these diagnoses of bronchiolitis, some are non-specific and not caused by RSV. However, RSV is the most common pathogen identified in infants with LRTI,¹ so it is expected that the overall burden of LRTI disease is reduced by nirsevimab, even when medical attention is not required.²²

Our results are in line with the 77.3% (95% CI: 50.3% to 89.7%) efficacy against hospitalisation for RSV shown in randomised clinical trials.⁸ Considering that only a few countries have introduced immunisation with nirsevimab this season, studies on its effectiveness are scarce. Our finding on nirsevimab effectiveness in preventing hospital admissions due to RSV is consistent with other works. A study conducted in some hospitals in other regions of Spain demonstrates effectiveness against RSV hospital admissions similar to ours, ranging between 70% and 84%.²³ Similarly, a report from the Centers for Disease Control and Prevention found a 90% reduction in RSV-associated hospitalisation,²⁴ and reports from Galicia show great reductions in 2023–2024 season compared with previous seasons in RSV hospital admissions in infants born between April and September.²⁵ Additionally, in Luxembourg, researchers observed reductions in hospitalisation of approximately 69%.²⁶ Nevertheless, our study adds value by complementing previous research with a primary care perspective.

Our study has some limitations. The observational nature of our data may have led to some type of confounding. Nevertheless, our analysis of a negative control outcome suggested comparability of the cohorts. Due to administrative and data registration delays, we were unable to include infants born after 30 September 2023 in our analysis. These infants would be the youngest during the RSV epidemic and therefore the ones most likely to benefit from immunisation with nirsevimab. We anticipate that data on these children will become available in the future, allowing us to complement our work in further research. Despite this limitation, our study provides valuable and timely insights into the effectiveness of nirsevimab across multiple outcomes for infants who were less than 6 months old before the onset of the RSV epidemic. Our study did not undertake an analysis of potential adverse effects; hence, it is imperative that future studies with appropriate designs be conducted to explore this aspect further. Additionally, the fact that in some settings, the majority of bronchiolitis cases are recorded as non-specific may lead to an underestimation of the effectiveness of less specific outcomes. Finally, changes in the community transmission of RSV during the study period could have a differential effect on the number of outcomes recorded in each cohort. However, our Cox regression model using a calendar time scale approach has been identified as an unbiased method for analysing outcomes with time-varying incidence and rapid uptake of immunisations.¹⁹

This study also boasts several strengths. The comprehensive linkage and coverage within our database, incorporating outcomes from both primary and hospital care, is unprecedented. Additionally, Catalonia's universal healthcare system, supported by centralised health databases, previously used in vaccine research studies,^{27,28} maximises the completeness of outcome ascertainment. Finally, our study period encompasses the entirety of the 2023–2024 RSV epidemic wave (online supplemental figure 1A).

In conclusion, nirsevimab has demonstrated significant effectiveness in protecting infants against a wide range of outcomes associated with RSV infection. These early real-world data provide valuable insights into the effects of nirsevimab in mitigating the burden of RSV-associated disease in infants. Moreover, they offer essential evidence to inform public health

authorities and guide decision-making processes regarding the implementation and prioritisation of RSV immunisation campaigns.

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1 vez dia¹

Zimbus[®] breezhaler[®]

Indacaterol, glicopirrônio, furoato de mometasona
pó para inalação, cápsulas



1ª associação
LABA/LAMA/ICS
indicada na ASMA⁴
Dose fixa diária¹

NOVA
ASSOCIAÇÃO
LABA/LAMA
/ICS¹

Dá ritmo à vida^{2,3*}

Para adultos com ASMA moderada a grave não controlados adequadamente com LABA/ICS.¹

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Zimbus Breezhaler 114 microgramas/46 microgramas/136 microgramas pó para inalação, cápsulas

NOTA: Antes de prescrever consulte o RCM do medicamento. APRESENTAÇÃO: Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrônio e 160 microgramas de furoato de mometasona. Cada dose libertada (a dose libertada através do aplicador bucal do inalador) contém 114 microgramas de indacaterol (na forma de acetato), 8 microgramas de brometo de glicopirrônio equivalente a 46 microgramas de glicopirrônio e 136 microgramas de furoato de mometasona. **Excipiente(s) com efeito conhecido:** Cada cápsula contém 25 mg de lactose mono-hidratada. **INDICAÇÕES:** Zimbus Breezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista beta₂ de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Compromisso renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncoespasmo, para os quais é necessário um broncodilatador de curta ação. ♦ **Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Breezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Broncoespasmo paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncoespasmo paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Efeitos cardiovasculares:** Tal como outros medicamentos contendo agonistas adrenérgicos beta₂, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose) e em doentes com resposta aumentada aos agonistas adrenérgicos beta₂. ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta₂ podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta₂ e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitem de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalarem a dose prescrita. ♦ **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingóides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hipercalcaemia, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais como o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraoculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta₂, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta₂ (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização ♦ **Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. ♦ **Tratamento hipocalcémico:** O tratamento hipocalcémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico dos agonistas adrenérgicos beta₂. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta₂ de ação prolongada:** A coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos beta₂ de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de cationes orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS:** ♦ **Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonia, gastroenterite, dor musculoesquelética, espasmos musculares, pirexia. ♦ **Pouco frequentes (≥0,1% a <1%):** hiperglicemia, cataratas, boca seca, erupção cutânea, prurido, disúria. Para mais informações, consultar o titular de autorização de introdução no mercado ou o representante local do titular de autorização de introdução no mercado. Medicamento sujeito a receita médica. **Escalação de comparticipação:** Escalão B. **Titular da AIM:** Novartis Europharm Limited. **Representante local:** Laboratório Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N° 29, Venda Nova, 2700-451 Amadora Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).

ARTIGO ORIGINAL

Custos diretos e indiretos da asma pediátrica no Reino Unido: uma análise de custos

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RESUMO

Objetivo Estimar o custo da asma pediátrica na perspectiva do Serviço Nacional de Saúde do Reino Unido (NHS) e da sociedade e explorar os fatores determinantes destes custos.

Desenho Análise de custos baseada em dados de um grande ensaio clínico entre 2017 e 2019. Os formulários de notificação de casos registraram a utilização de recursos de saúde e as perdas de produtividade atribuíveis à asma durante um período de 12 meses. Estes foram combinados com dados nacionais de custos unitários para gerar estimativas de serviço de saúde e custos indiretos.

Contexto Clínicas de asma nos cuidados primários e secundários em Inglaterra e na Escócia.

Principais resultados Custo por ataque de asma estratificado pelo nível mais elevado de cuidados recebidos. Total anual do serviço de saúde e dos custos indiretos. Efeito modelado de sexo, idade, gravidade, número de ataques e adesão sobre os custos anuais totais.

Resultados Das 506 crianças incluídas na análise, 252 sofreram pelo menos um ataque. O custo médio (DP) por ataque foi de £297 (806) (mediana £46, IQR 40–138) e o custo total anual médio para o NHS foi de £1086 (2504) (mediana £462, IQR 296–731). Em média, as crianças faltaram 6 dias à escola e os seus cuidadores faltaram a 13 horas de trabalho remunerado, contribuindo para um custo indireto anual médio de £412 (879) (mediana £30, IQR 0–477). Os custos do serviço de saúde aumentaram significativamente com o número de ataques e com a idade dos participantes (>11 anos). Os custos indiretos aumentaram com a gravidade da asma e o número de crises, mas foram inferiores nas crianças mais velhas.

Conclusões A asma pediátrica representa um encargo económico significativo para o serviço de saúde, para as famílias e para a sociedade. Os esforços para melhorar o controlo da asma podem gerar reduções de custos significativas.

Número de registo do ensaio ISRCTN 67875351.

INTRODUCTION

Asthma affects between 5% and 10% of children in the UK.^{1–3} Asthma attacks are common, can be life threatening and impose a considerable economic burden on the health service, families and society.^{4–7} It has been estimated that provision of care for all patients with asthma costs the National Health Service (NHS) £3.03 billion per year.⁶

The cost of asthma is known to be associated with severity and control; more severe and less controlled asthma is linked to the greatest healthcare resource use (HCRU).^{8–10} There is a lack of recently published studies that have quantified the economic burden that paediatric asthma imposes on the health system and society in the UK. This may limit the ability of planners and commissioners to accurately budget for the delivery of asthma services or determine the potential value of initiatives to improve its control. To address this

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Direct and indirect costs of paediatric asthma in the UK have not been estimated for many years.
- Older data indicate that costs to the health service are higher for those with more severe and uncontrolled asthma due to an increased requirement for hospital care.
- The condition is associated with considerable indirect costs arising from days missed from school and carers having to take time off work to care for children.

WHAT THIS STUDY ADDS

- This study provides detailed contemporary healthcare resource use and productivity loss estimates resulting from paediatric asthma over a 1-year period, and quantifies their relationship with patient and disease characteristics.
- Annual costs to the health service are more than threefold higher for children who experience three to four attacks compared with those with no attacks.
- Productivity losses are 1.7 times higher for families of participants with more severe (British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) step 4) versus less severe (BTS/SIGN step 2) disease, and 6.7 times higher for those who experience three to four attacks per year compared with no attacks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study highlights the potential economic savings of improved asthma treatment to reduce the number of attacks.
- The estimates of resource use and cost can serve as key inputs to service planning and future economic modelling studies of asthma interventions and initiatives.

evidence gap, we use data collected from a randomised controlled trial (RCT) which recruited children with asthma between 2017 and 2019 to describe the direct and indirect costs of childhood asthma in the UK.

METHODS

Study design

The Reduced Asthma Attacks in Children using Exhaled Nitric Oxide (RAACENO) trial recruited 509 children from centres across the UK between 2017 and 2019, the majority (97%) from secondary care. Participants were aged 6–15 years, diagnosed with asthma, treated with inhaled corticosteroids and had at least one asthma attack in the past year. The trial found no evidence for a difference in clinical outcomes or costs between the randomised treatment groups (FeNO plus symptom-guided treatment or symptom-guided treatment alone), justifying the pooling of data for this cost analysis. Full details of the trial results, objectives and design are available elsewhere.¹¹

Data collection

Data were collected retrospectively from parent-held diaries and case report forms (CRFs) completed during four clinic assessments at 3-month intervals throughout the follow-up period. The information relevant to this analysis included asthma medications, treatment adherence, number of asthma attacks and associated healthcare use, other asthma-related healthcare use and participant and carer time lost from usual activities.

Cost estimation methods

The analysis took a UK NHS perspective for HCRU and a societal perspective for time losses. All costs are expressed in 2019/2020 UK sterling using the NHS inflation indices where necessary.¹² The costs incurred during each quarterly time interval were summed at the individual level across all observations over the 1-year follow-up period.

Three categories of asthma-related HCRU were identified from the CRFs: (1) HCRU associated with attacks; (2) HCRU not associated with attacks; and (3) medication. Direct NHS costs under each category were calculated by multiplying the reported HCRU by nationally representative unit costs (online supplemental table 1).^{12–14} Staff time required for pharmacist and NHS 111 contacts were informed by external literature.^{15 16} The cost of medications was sourced from the British National Formulary (BNF) and combined with the prescribed dose (online supplemental table 2).¹⁷ An NHS confidential discount is available for omalizumab injections. For this analysis we used the list price.¹⁸

Indirect costs were measured using the human capital approach.¹⁹ Time displaced was categorised as: school, leisure, study and paid or unpaid work. Details of the unit costs applied to time losses are presented in online supplemental material 1.

Statistical analysis

Data were summarised using the mean, SD, median and IQR for continuous variables, and numbers and percentages for categorical variables. While healthcare cost data are often right skewed, whereby a minority of high-resource patients lift the mean above the median, the analysis and interpretation focuses on the mean as the most relevant measure of budgetary impact.²⁰ All analyses were conducted using STATA V.15.²¹

Missing data were minimised by asking about patient-reported resource use and time losses at each attended clinical assessment visit, covering the time elapsed since the last attended visit. If patients failed to attend their final follow-up assessment, they were followed by phone to collect data on all attacks and associated resource use. We assessed the sensitivity of results to missing data using multiple imputation with chained equations.²²

Generalised linear models (GLM) were used to explore the effect on total cost of several covariates: age, sex, asthma severity, number of attacks and treatment adherence. Age was categorised as per the minimisation criteria used in the RAACENO trial (<11 years; ≥11 years). Asthma severity was categorised by level of asthma medication using the British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN) step system.²³ Adherence was measured on a scale between 0 and 1 (online supplemental material 2 and online supplemental table 3), with a value of ≥70% defined as adherent. The number of attacks was categorised as 0, 1–2, 3–4 or ≥5, to allow for non-linearity in the relationship between number

of attacks and cost. The cost of study assessment visits was excluded from the GLM analysis of direct health service costs, as these were potentially protocol driven and invariable between patients. GLM results are expressed in terms of the average effect of each variable on the model's predicted cost. Given the skewed nature of the data, gamma family and log link functions were specified based on findings of modified Park and Box-Cox tests of functional form.^{24 25} A high proportion of zero values were observed for indirect costs, which creates challenges for statistical modelling. A two-part model was specified with a probit model first used to predict the probability of reporting time losses combined with a GLM model to predict costs among those with time losses.²⁶ These models are combined to estimate the effects of covariates on total indirect costs. Both models used robust SEs clustered by centre number. The trial was registered with the ISRCTN registry (ISRCTN 67875351).

RESULTS

Baseline characteristics

There were 509 participants recruited of whom 506 were included in the analysis. We have previously shown that the RAACENO participants were comparable to children attending secondary care asthma clinics in the UK.¹¹ Most patients (85%) were on step 3 or step 4 BTS/SIGN treatment levels and 56% had an inpatient admission for asthma in the year preceding recruitment (table 1).

Direct cost to the health service

Attacks

There were 509 attacks observed in 252 participants during follow-up. Associated HCRU data were available for 244 participants (497 attacks), with 49 (61 attacks) requiring inpatient hospital admission. The mean cost per attack was £297 (SD: 806) and the median was £46 (IQR: 40, 138). Table 2 presents the cost per attack overall and by the highest level of care received. The average number of healthcare contacts is provided in online supplemental table 4. Most attacks (n=291) were treated in primary care, predominantly by a general practitioner. Where secondary care was required, participants were typically treated in the emergency department, followed by hospital inpatient admissions. No healthcare contact was made for 46 attacks (29 participants) which were treated with a course of oral steroids available at home. Results by treatment group are provided in online supplemental table 5.

Total HCRU

Besides attack-related HCRU and study follow-up assessments, a large proportion of participants (n=225/443) did not report any additional HCRU. Table 3 reports the mean total cost of asthma-related HCRU over the trial follow-up period. The mean cost of asthma is driven by participants who had multiple attacks, required inpatient hospitalisation and were prescribed high-cost omalizumab (n=13/432). All participants used a preventer (inhaled corticosteroid±long-acting beta agonist) and reliever inhaler. Other medication use included leukotriene receptor antagonist (n=287/432), theophylline (n=50/432) and ciclosporin (n=6/432). A detailed breakdown of cost by treatment group and corresponding HCRU is found in online supplemental tables 6 and 7.

Indirect cost

Table 4 summarises participant-reported time losses from productive activities and corresponding indirect costs for those reporting time losses. Most participants reported missing days of school due to asthma. Approximately half (52%) of adult family and carers reported time losses, mostly from paid employment. The mean indirect cost in the population, inclusive of those reporting zero time losses, was £412 (SD: 879). The median was £30 (IQR: 0, 477). On average, participants reported missing 5.9 (SD: 8.5) days of school. Results by treatment allocation group are provided in online supplemental table 8.

Determinants of total direct and indirect costs

The results from GLMs of direct and indirect costs are presented in table 5, in terms of the effect of each explanatory variable

Table 1 Baseline characteristics

	N	n/Mean	%/SD	Median	IQR
Sex, male (n, %)	506	306	60.5		
Age, years (mean, SD)	506	10.1	2.6	10	(8, 12)
<11 (n, %)	506	285	56.3		
≥11 (n, %)	506	221	43.7		
Age at diagnosis, years (mean, SD)	503	3.8	2.6	3	(2, 5)
Weight, kg (mean, SD)	502	39.9	16.4	36.7	(27.6, 48.6)
Centre, secondary (n, %)	506	490	96.8		
Treatment level* (n, %)					
BTS/SIGN step 2	506	76	15.0		
BTS/SIGN step 3	506	217	42.9		
BTS/SIGN step 4	506	213	42.0		
Controlled† (n, %)	506	256	50.6		
Hospital admissions in the last year (n, %)					
None	506	221	43.7		
1–2	506	201	39.7		
3–4	506	55	10.9		
≥5	506	29	5.7		
Days absent from school in the last year (mean, SD)	504	15.0	14.4	10	(4.8, 20.0)
Oral steroid courses in the last year, count (mean, SD)	506	3.6	3.0	3	(1, 5)
Prescription details					
LTRA (n, %)	506	303	59.9		
Reliever inhaler (n, %)	506	506	100		

*Treatment levels based on the British Guideline on the Management of Asthma.²³

†Asthma Control Test score ≥20.

BTS, British Thoracic Society; LTRA, leukotriene receptor antagonist; SIGN, Scottish Intercollegiate Guidelines Network.

Table 3 Total healthcare resource use costs observed during trial follow-up

Category (patients contributing data (N))	Patients reporting any resource use (n (%))	Mean*	SD	Median*	IQR
Total including clinical study visits (N=430)†	430 (100)	£1846	2514	£1230	(1055, 1518)
Total excluding clinical study visits (N=430)	430 (100)	£1086	2504	£462	(296, 731)
Attack related (N=498)	244 (49.0)	£604	1284	£140	(57, 393)
Primary care	206 (41.4)	£101	99	£79	(40, 119)
Secondary care	115 (23.1)	£1095	1698	266	(133, 1906)
Oral steroid	244 (49.0)	£3.36	4.45	£2.11	(0.36, 4.78)
Not associated with attacks (N=443)	218 (49.2)	£295	650	£133	(40, 250)
Primary care	178 (40.2)	£90	90	£50	(40, 114)
Secondary care	102 (23.0)	£476	888	£204	(133, 408)
Medication‡	4 (0.9)	£1.75	0.00	£1.75	(1.75, 1.75)
Medication for asthma management (N=432)	432 (100)	£647	2092	£345	(234, 433)
Immunoglobulin injections (omalizumab)	13 (3.0)	£10 824	5592	£11 150	(4520, 14 736)
Clinical study visits (N=506)†	481 (95.0)	£721	167	£816	(612, 816)

*Cost for those incurring any resource use (excluding those with zero cost).

†Quarterly clinical study visits were excluded from the regression analysis of cost determinants.

‡In addition to medication prescribed at regular monitoring visits for the participant's asthma.

on modelled cost. The direct cost model predicts costs of £2841 (SE: 658) for patients ≥11 years old with more severe asthma (BTS step 4) who experience ≥5 attacks in the year. Patients <11 years old, with less severe asthma (BTS step 2), who experience no attacks, are predicted to cost the NHS £521 (SE: 137). A similar pattern was observed for indirect cost, but with a negative association for age. The probability of reporting no time losses was 0.65 (SE: 0.04, $p<0.01$) if the participant experienced no attacks.

The mean adherence was 72.5% (SD: 20.0). Adherence was found to be predictive of direct cost ($p=0.03$); adherent patients were projected to cost £464 (SE: 298) more than non-adherent. Previous asthma studies^{27–28} defined 'adherent' as ≥80%. Under this definition, adherence was not found to be a predictor of direct cost ($p=0.93$). The estimates were robust to missing data assumptions, with similar results obtained using multiple imputation. In a further sensitivity analysis which removed participants who received omalizumab, the effects of age and adherence on direct costs were no longer significant, and the predicted annual direct costs were substantially lower (£728) (online supplemental table 9).

Table 2 Healthcare cost associated with each attack stratified by highest level of care received

	All		Primary		Secondary		At home*	
Number of participants (N=244/252)†	244		171		115		29	
Number of attacks (N=497/509)‡	497		291		160		46	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total cost per attack	£297	806	£57	52	£819	1271	£1.41	2.63
Primary care	£42	51	£55	52	£30	47		
GP	£31	33	£42	27	£21	39		
Nurse	£2.03	8.19	£2.09	8.42	£2.52	8.87		
NHS 24/111	£1.07	4.92	£1.07	5.97	£1.38	4.01		
Out-of-hours GP service	£5.66	37	£7.63	47	£3.70	18		
Walk-in centre	£1.75	9.69	£2.36	11	£1.14	7.16		
Pharmacist	£0.03	0.43	£0.02	0.40	£0.04	0.54		
Secondary care	£253	812			£787	1277		
Emergency department	£23	54			£71	74		
Hospital outpatient	£4.21	26			£13	45		
Hospital inpatient	£220	814			£684	1323		
Day case	£1.58	25			£4.92	44		
Ambulance	£4.56	37			£14	64		
Medication	£1.65	1.95	£1.66	1.81	£1.71	1.99	£1.41	2.63

*One-week course of 5 mg prednisolone per day.

†N=patients with attacks with complete resource use data/observed number of patients with attacks.

‡N=attacks with complete resource use data/observed attacks.

GP, general practitioner; NHS, National Health Service.

Table 4 Indirect costs of asthma captured over the trial follow-up

Category (patients contributing (N))	Patients reporting any time losses (n (%))	Mean*	SD	Median*	IQR
Days displaced (child) (N=443)	333 (75.2)	8.2	9.2	5	(2, 11)
School	332 (74.9)	7.9	9.0	5	(2, 11)
Paid employment	45 (10.2)	2.6	2.3	2	(1, 3)
Hours displaced (adults†) (N=443)	225 (50.8)	56	85	26	(12, 60)
Paid employment	161 (36.3)	36	42	20	(8, 44)
Unpaid work	103 (23.3)	45	71	18	(7, 56)
Leisure	58 (13.1)	29	51	8	(4, 25)
Study	24 (5.4)	21	29	8.5	(4, 23)
Indirect costs (child)‡ (N=443)	45 (10.2)	£90	80	£70	(35, 104)
Indirect costs (adults†) (N=443)	219 (49.4)	£816	1096	£470	(159, 936)
Paid employment	161 (36.3)	£709	837	£397	(159, 874)
Unpaid work	103 (23.3)	£543	854	£216	(84, 673)
Leisure	58 (13.1)	£148	257	£40	(20, 126)
Total cost (N=443)	229 (51.7)	£798	1090	£451	(159, 914)

*Cost reported for those incurring any resource use (excluding those with zero cost).

†Any adult relative or carer of the participant.

‡Does not include indirect costs associated with time losses from education.

DISCUSSION

This study provides detailed estimates of the cost of paediatric asthma from both the NHS and societal perspective, for a population prone to attacks, followed up mainly in secondary care. The cost per attack to the health service (£297) was driven by hospital inpatient admissions, despite only 12% of attacks leading to admission. The mean cost to the health service was £1086 per participant over the 12-month follow-up period, inclusive of £647 for medication, £296 of attack-related resource use and £145 for other resource use. Participants missed on average 5.9 (SD: 8.5) days of school and parents and carers missed 13.0 (SD: 30.6) hours of work in relation to the child's asthma. These find-

ings highlight the often unrecognised costs of asthma to children and families.

The higher direct cost for older relative to younger children and the unexpected finding of higher cost for adherent compared with non-adherent children can be explained by omalizumab prescribing being clustered in more adherent children over the age of 11, at a cost of up to £18 078 per year based on the list price. Just 13 participants received this medication, 10 of whom were >11 years old and had adherence >70%. Adherence and age were no longer predictive of direct costs when these participants were removed from the analysis. The finding of lower indirect costs for older participants may be explained by families becoming more knowledgeable of the condition as children age, and therefore better able to manage it without taking time off work. We also know that severity and control improve as children age,^{29 30} so we may be observing a mediation between asthma severity and age.

A strength of this analysis is that it is based on data from a large multicentre RCT conducted in England and Scotland. A high degree of complete data was achieved, particularly in relation to attack-related resource use. The number of attacks, hospitalisations and school days missed were substantially higher in the year preceding randomisation. It is unclear if such improvement would be achieved outside the trial setting, meaning that 'real world' costs might be higher. Data may be subject to protocol biases as participants attended clinical assessments more regularly than in routine practice and may have had better control as a result. It would be of value to externally validate these findings using observational data. Nevertheless, our estimated cost per attack, and effects of covariates on direct and indirect costs, should be generalisable to the wider paediatric asthma population. A further weakness is that our study did not collect information regarding attack severity. There is scope to better understand the determinants of attack cost to the NHS given the high variability observed. There are also limitations of how adherence was measured and defined, with some discrepancies between different sources leading to uncertainty regarding its accuracy. Finally, our estimate of indirect costs is restricted to productivity losses arising from absenteeism. It does not capture presenteeism so may underestimate the full indirect costs of asthma.

There is a paucity of contemporary studies reporting on the cost of paediatric asthma in the UK.^{8 10} Kerkhof et al reported a mean

Table 5 Results of the GLM model of direct health service costs and the two-part model of indirect costs presented in terms of predictive margins and average marginal effects

Covariates	Direct cost (N=430)					Indirect cost (N=443)				
	Predictive margins	SE	Marginal effect	SE	P value*	Predictive margins	SE	Marginal effect	SE	P value*
Predicted cost	£1104	250				£415	45			
Sex										
Male	£1208	340				£405	60			
Female	£961	146	−£247	235	0.20	£431	53	£26	73	0.86
Age (years)										
<11	£885	162				£509	64			
≥11	£1423	425	£538	303	<0.01	£293	50	−£217	74	<0.01
Treatment level†										
BTS/SIGN step 2	£974	236				£275	52			
BTS/SIGN step 3	£1122	431	£148	426	0.72	£393	51	£118	66	0.06
BTS/SIGN step 4	£1113	153	£139	272	0.62	£465	80	£191	87	<0.01
Number of attacks										
0	£736	259				£144	28			
1–2	£1138	262	£402	122	<0.05	£504	60	£361	64	<0.01
3–4	£2302	588	£1565	562	<0.01	£985	185	£841	185	<0.01
≥5	£2188	434	£1452	417	<0.01	£1114	289	£970	281	<0.01
Adherence										
Not adherent (<70%)	£807	86				£317	60			
Adherent (≥70%)	£1271	354	£464	297	<0.05	£464	54	£146	70	0.11

*P value from generalised linear model (GLM) regression.

†Treatment levels based on the British Guideline on the Management of Asthma.²³

BTS, British Thoracic Society; SIGN, Scottish Intercollegiate Guidelines Network.

annual HCRU cost of £861 (2015 prices) for patients with severe, uncontrolled eosinophilic asthma. Our estimate for secondary care managed paediatric asthma, inclusive of quarterly clinical assessment visits, is higher at £1846. This may be explained by differences between the study populations—only 2% of the population reported by Kerkhof et al were under 18 years of age—and more intensive routine monitoring within the RAACENO trial. Gokhale et al⁸ assessed the HCRU of 265 paediatric asthma patients aged 6–17 years in England who had severe refractory asthma. During a 1-year period, 42.6% of patients experienced at least one oral corticosteroids (OCS)-defined attack (excluding attacks treated at home), and 24.5% of attacks resulted in a hospital attendance. In RAACENO, we found that 48.6% (242/498) of participants experienced at least one attack requiring contact with primary or secondary care, with 35.5% of these resulting in secondary care contact.

Our results with respect to productivity losses are broadly consistent with those reported in the literature. Based on a review of published evidence, Nunes et al reported that a child experiencing an exacerbation can expect to miss 3–5 days of school, with parents missing a similar number of days of work.⁵ RAACENO participants experienced two attacks on average. Those who experienced at least one attack reported missing 9.4 (SD: 10.3) days of school and their carers reported missing 20.9 (SD: 39.2) hours of paid work.

The results of this study can support the planning of asthma services for similar populations. This is directly relevant to initiatives to improve asthma care and outcomes in the NHS such as phase 1 of the National Bundle of Care for Children and Young People with Asthma.³¹ It is estimated there are currently 1.1 million children receiving treatment for asthma in the UK.³² A recent UK-based cohort study of children with asthma in primary care suggests an annual attack rate of at least 0.18 per patient-year.³³ Assuming our cost per attack estimate is generalisable to attacks experienced by the wider paediatric asthma population, the expected annual cost of asthma attacks would be in the region of £59.2 million at the population level (1.1M × 0.18 × \$297). Acknowledging the caveats around generalisability of hospitalisation rates for attacks observed in the RAACENO study, this simple calculation illustrates how our results could be used to inform service planning and future modelling initiatives.

In conclusion, paediatric asthma imparts a significant economic burden on the health service, families and society. Our data provide a useful input to future studies that seek to model the broader costs and savings of efforts to improve paediatric asthma control and reduce attack frequency.

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Fibrose Quística: um diagnóstico para a vida

Considerada uma doença rara, a Fibrose Quística (FQ) afeta cerca de 75.000 pessoas em todo o mundo. Trata-se de uma doença genética que afeta principalmente os pulmões e o sistema digestivo. Caracteriza-se pela produção de secreções espessas e viscosas que, condicionam obstrução brônquica e dos canais pancreáticos e de outros órgãos, resultando em infeções pulmonares de repetição e dificuldades na digestão.

Em Portugal, existem cerca de 400 doentes com Fibrose Quística. A doença é classificada como autossómica recessiva, o que significa que ambos os pais devem ser portadores do gene defeituoso para que o filho a desenvolva a doença. Estima-se que a nível mundial existam 7 milhões de pessoas portadoras da anomalia genética da FQ. Entre os sintomas mais comuns estão tosse crónica com expetoração muito abundante, dificuldade respiratória, infeções respiratórias de repetição, perda de peso, e dificuldade na digestão. Além disso, alguns doentes apresentam também complicações como diabetes associada à FQ entre outras.

É uma doença que sem tratamento adequado dirigido à correção do defeito proteico interfere profundamente com a qualidade de vida dos doentes e tem um forte impacto negativo na sobrevida.

O seguimento dos doentes em Centros de Referência por equipas altamente especializadas, o rastreio neonatal e o recurso a terapêuticas moduladoras da proteína CFTR de alta eficácia, veio modificar de forma bastante positiva o panorama da doença permitindo uma melhoria substancial da qualidade de vida e um aumento muito expressivo da sobrevida. Estes aspetos têm conduzido a uma modificação no paradigma de seguimento destes doentes, permitindo o recurso a modelos de atendimento por telemedicina e impondo a inclusão nas equipas de especialistas vocacionados para o tratamento das doenças associadas ao envelhecimento particularmente do foro cardiovascular e oncológico.

Em Portugal existem cinco Centros de Referência distribuídos pelo País, o rastreio neonatal encontra-se implementado desde 2013 e a nova terapêutica tripla de alta eficácia para correção do defeito da proteína CFTR está disponibilizada com comparticipação total pelo SNS desde 2021.

Contudo, existem ainda alguns doentes cujo genótipo não os torna elegíveis para beneficiar da nova terapêutica modificadora da doença ou que desenvolvem sintomas adversos que obrigam a suspender esta terapêutica. Este grupo de doentes constitui um importante desafio, obrigando a um acompanhamento muito rigoroso e ao recurso a exigentes medidas terapêuticas sintomáticas que incluem cinesiterapia respiratória, terapêutica fluidificante das secreções brônquicas, terapêutica broncodilatadora e anti-inflamatória, terapêutica de substituição enzimática pancreática, suplementação vitamínica, insulinoaterapia e transplante pulmonar. São terapêuticas muito exigentes e dispendiosas e que requerem uma disciplina férrea. A investigação prossegue no sentido de encontrar novas soluções terapêuticas que possam beneficiar também estes doentes.

O futuro mostra-se pois promissor e juntos só descansaremos quando todos os doentes com Fibrose Quística puderem beneficiar de uma solução terapêutica que assegure uma sobrevida longa e com qualidade.

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ARTIGO ORIGINAL

A humidade visível no quarto de uma criança está associada a um aumento da morbilidade respiratória no início de vida: um estudo de coorte multicêntrico

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RESUMO

Objetivo A exposição à humidade doméstica é um importante problema de saúde pública. O nosso objetivo foi avaliar o impacto da localização da humidade doméstica nos resultados respiratórios durante os primeiros anos de vida.

Métodos A exposição à humidade doméstica foi verificada em crianças recrutadas para o estudo de coorte de nascimentos multicêntrico GO-CHILD. A frequência de sintomas respiratórios, infeções, utilização de cuidados de saúde e prescrição de medicação para a pieira foi recolhida por questionários enviados por correio postal aos 12 e 24 meses. Os dados foram ajustados a modelos de regressão logística binomial e ordenada.

Resultados 1344 crianças foram acompanhadas entre agosto de 2010 e janeiro de 2016. A humidade visível esteve presente num quarto das habitações (25,3%), com 1 em cada 12 quartos de criança a serem afetados (8,3%). A humidade na casa de banho, na cozinha ou na sala de estar não esteve associada a quaisquer resultados respiratórios nem relacionada com infeções. A humidade no quarto da criança foi associada a um risco acrescido de tosse seca (8,7% vs. 5,7%) (risco relativo ajustado 1,56, IC 95% 1,07 a 2,27; $p=0,021$) e a probabilidade de recorrer a cuidados primários devido a tosse e pieira (7,6% vs. 4,4%) (OR ajustado 1,37, IC 95% 1,07 a 1,76; $p=0,009$). Também se verificou um aumento do risco de prescrição de corticosteroides inaláveis (13,3% vs. 5,9%) (RR ajustado 2,22, IC 95% 1,04 a 4,74; $p=0,038$) e de inaladores de alívio (8,3% vs. 5,8%) (RR ajustado 2,01, IC 95% 1,21 a 2,79; $p=0,018$).

Conclusão A humidade no quarto das crianças esteve associada a um aumento da morbilidade respiratória. Em crianças que apresentam sintomas respiratórios recorrentes, os médicos devem investigar a existência e a localização da humidade, cuja presença pode ajudar a definir as prioridades das famílias que necessitam de uma avaliação urgente da humidade doméstica e de obras de reparação.

INTRODUCTION

The burden of preschool wheeze and cough is a prominent public health issue that appears to be increasing in prevalence and is associated with significant morbidity, healthcare utilisation and cost.¹ The aetiology of preschool wheeze and cough, and childhood asthma is a complex interplay between host genetics and environmental factors that may be modifiable.²

There is compelling evidence from a series of meta-analyses and systematic reviews that early life exposure to household damp is associated with respiratory symptoms and subsequent diagnosis of asthma.^{3,4} There has been a renewed focus on the harmful impact of damp in the UK after the tragic death of Awaab Ishak in 2020 following mould inhalation from extensive damp in the family's

Key messages

What is the key question?

- Household damp is a major public health challenge with 1.6 million children in England estimated to be living in affected properties.
- Damp exposure in early childhood is associated with increased respiratory symptoms and subsequent diagnosis of asthma.

What is the bottom line?

- Visible damp in a child's bedroom but not elsewhere in the household is associated with primary care attendance for cough and wheeze as well as inhaled steroid and reliever inhaler prescription.
- The location of damp within the household may be an important determinant of the impact of mould on children's respiratory health.

Why read on?

- Health professionals should enquire about both the presence and location of household damp in children presenting with recurrent respiratory symptoms.
- The presence of visible damp in a child's bedroom could be used to help identify those families most urgently in need of targeted household damp treatment by the local government.

home. Awaab's law was introduced as part of the Social Housing (Regulation) Act 2023 and requires social housing landlords in England to investigate and treat damp issues.

Household damp is a substantial public health problem with an estimated 1.6 million children in England living in affected properties.⁵ Tackling this potentially preventable cause of significant respiratory morbidity in children is vitally important and identifying which household rooms affected by damp are most associated with respiratory outcomes could allow remediation work to be efficiently targeted. The aim of our study was to assess the impact of the location of household visible damp on respiratory symptoms, infections, healthcare utilisation and medication prescription for wheezing during the first 2 years of life.

METHODS

Pregnant women were recruited to the GO-CHILD prospective birth cohort study between August 2009 and November 2013 from throughout England and Scotland to investigate the role of environmental and gene variation on respiratory outcomes in young children. Postal questionnaires were completed at 12 and 24 months to determine household damp exposure and respiratory symptoms and outcomes (see online supplemental file 1 for questionnaires). Carers provided informed consent.

Exposure and outcomes

Carers were asked whether there was visible damp within the house and whether damp was present in the bathroom, kitchen, living room or the child's bedroom. The frequency of respiratory symptoms (wheeze and cough), healthcare utilisation (primary care attendance, emergency department attendance and secondary care referral) and medication prescriptions (reliever inhaler, inhaled and oral corticosteroid) for wheeze were recorded. The frequency of respiratory infections (bronchiolitis, pneumonia, otitis media and cold or influenza) were also recorded.

Statistical analysis

Data on children whose carers had completed at least one follow-up questionnaire were included in the analysis. The data was reshaped into a long format to enable analysis of repeated measures. A cluster variance estimator adjustment was made to the SEs to take account of repeated measures. Log binomial regression was used for binary outcomes. Ordinal logistic regression was used for ordered grouped counts. A regression analysis was performed for each of the 12 clinical outcomes. On the basis of existing knowledge and following discussion with the GO-CHILD study team, models were adjusted for: the mother's level of education; daycare attendance; breast feeding beyond 6 months; siblings at home; environmental tobacco smoke exposure; child's bedroom flooring (as a surrogate of house dust mite); animal exposure; road traffic density (traffic pollution) around child's home (little/moderate/dense); and solid fuel pollution within the home (see online supplemental file 2 for confounder analyses). A two-sided p value of <0.05 was deemed statistically significant for all analyses. Stata (StataCorp 2019 Stata Statistical Software: Release 16 College Station, Texas: StataCorp) was used for all statistical analyses. Our study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology principles⁶ for reporting cohort studies.

RESULTS

Data were collected from August 2010 to January 2016. 1344 children were included in the analyses with at least 1 carer follow-up question-

naire completed (figure 1). Visible damp was present in over a quarter of homes (25.3%) and was most common in the living room (15.1%), bathroom (12.2%) and children's bedroom (8.3%). Visible damp was present in the bedroom only in 10.9% of the 340 homes affected by damp. Demographic information, damp exposure, environmental factors and follow-up are summarised in table 1.

Damp in the child's bedroom was associated with an increased risk of dry cough (adjusted relative risk (RR) 1.56, 95% CI 1.07 to 2.27; p=0.021) and increased odds of primary care attendance for cough and wheeze (adjusted OR 1.37, 95% CI 1.07 to 1.76; p=0.009) (table 2). It was also associated with an increased risk of reliever inhaler (adjusted RR 2.01, 95% CI 1.21 to 2.79; p=0.018) and a greater than twofold increased risk of inhaled corticosteroid (adjusted RR 2.22, 95% CI 1.04 to 4.74; p=0.038) prescription (table 2). There was no association between the presence of damp in the bathroom, kitchen or living room with any respiratory or infection-related outcomes (online supplemental file 3).

DISCUSSION

Visible damp in the child's bedroom was associated with an increased risk of cough and wheeze requiring primary care review as well as the requirement for a reliever and steroid controller inhaler prescription. The location of damp within the household may be an important determinant of the impact of mould on children's respiratory health. The association with the child's bedroom is logical as this is the location where the child is likely to spend the greatest period of time and thus have the greatest potential duration of mould exposure.

Visible damp anywhere within the house in the GO-CHILD birth cohort has been reported previously.⁷ It was associated with an increased risk of dry cough, and increased odds of wheeze as well as primary care attendance for cough and wheeze. There was also an increased risk of reliever inhaler and inhaled corticosteroid prescription (online supplemental file 2).

Damp surfaces provide conditions favourable for the indoor growth of mould. *Penicillium* spp, *Cladosporium* spp, *Aspergillus* spp and *Alternaria* spp are common mould allergens found in houses with visible damp.⁸ It is hypothesised that these microscopic allergens can induce inflammation by releasing mycotoxins and by antigen-specific (IgE) mast cell activation.⁸ A series of meta-analyses and systematic reviews provide robust evidence that early life exposure to visible damp is associated with early asthma symptoms and later diagnosis of asthma.^{3,4} Early life damp exposure may have a long-term impact on respiratory health with an adverse impact on lung function growth in young people between aged 12 and 16 years identified⁹ as well as an increased risk of asthma at age 16.¹⁰

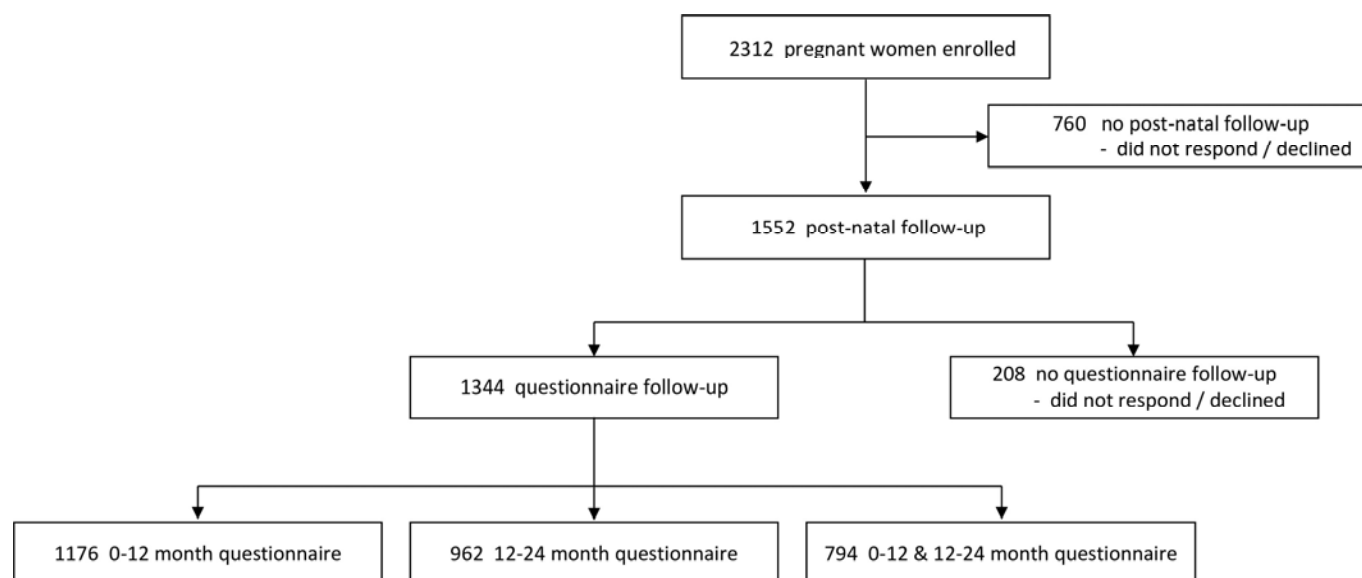


Figure 1 Study profile.

Table 1 Demographic information, damp exposure, environmental factors and follow-up

Gender (n=1344)	
Male	681 (50.7%)
Female	663 (49.3%)
Ethnicity (n=1344)	
Caucasian	1216 (92.5%)
Asian	33 (2.5%)
Black	21 (1.6%)
Mixed race	27 (2.1%)
Other	7 (0.5%)
Not reported	40
Visible damp in the house (n=1344)	
Damp in child's bedroom	111 (8.3%)
Damp in bathroom	164 (12.2%)
Damp in kitchen	78 (5.8%)
Damp in living room	203 (15.1%)
Damp anywhere in house	340 (25.3%)
Environmental factors (n=1344)	
Daycare attendance	782 (58.2%)
Breast fed >6 months	685 (51.0%)
Siblings	812 (60.4%)
Tobacco smoke	181 (13.5%)
Carpet in bedroom	1069 (79.5%)
Animals	765 (56.9%)
Dense traffic	125 (9.3%)
Solid fuel	142 (10.6%)
Maternal education level (n=1285)	
Completed primary education	58 (4.5%)
Completed secondary education	345 (26.8%)
Further education	388 (30.2%)
Higher education	494 (38.4%)
Not reported	59
Follow-up	
0–12 months questionnaire	1176
12–24 months questionnaire	962
0–12 and 12–24 months questionnaires	794
Questionnaire follow-up/included in analysis	1344
Environmental factors for the demographic table were taken from the first survey in preference to the second. Gender and ethnicity data relate to the child.	

The scale of the public health challenge of damp in UK housing is substantial with the regulator of Social Housing publishing a report in February 2023 estimating that up to 160 000 social homes in England (3–4%) were impacted by ‘notable’ damp and mould and an estimated 1.6 million children in England are living in affected properties.⁵

The government’s ambition to address household damp is clear with the introduction of Awaab’s law compelling landlords to address damp and mould in social homes. Citizen’s advice (www.citizensadvice.org.uk) and the charity Shelter (www.shelter.org.uk) provide comprehensive advice on dealing with damp and mould issues in private rented homes. Raising awareness among parents and health professionals of the health issues affecting children who live in damp environments is important. Our findings will be valuable in assisting health professionals in advocating for their vulnerable patients as well as helping local government prioritise action for families whose children’s bedrooms are affected by visible mould.

There are notable limitations that should be considered when assessing our study findings. Recall bias is an important consideration given the retrospective questionnaires used to determine symptoms, diagnoses and treatments. Misclassification bias is another potential limitation given diagnoses were carer-reported

Table 2 Presence of damp in a child’s bedroom and the occurrence of respiratory symptoms, healthcare utilisation, medication prescriptions and respiratory infections

		Damp in bedroom				
		0–12 months		12–24 months		
		No	Yes	No	Yes	
Wheeze	Yes	246	22	192	14	RR 1.16 (0.61 to 1.57) p=0.319
	No	860	48	708	48	
Dry cough	Yes	169	17	134	12	RR 1.56 (1.07 to 2.27) p=0.021
	No	937	53	766	50	
Primary care attendance for cough and wheeze	0	517	29	494	22	OR 1.37 (1.07 to 1.76) p=0.009
	1	288	24	214	19	
	2–3	228	14	138	17	
	≥4	66	3	45	4	
Emergency department attendance for wheeze	Yes	63	3	61	5	RR 1.29 (0.73 to 2.31) p=0.376
	No	1043	67	839	57	
Secondary care attendance for cough and wheeze	Yes	37	2	28	2	RR 1.47 (0.46 to 4.68) p=0.511
	No	1069	68	872	60	
Reliever inhaler	Yes	152	13	156	15	RR 2.01 (1.21 to 2.79) p=0.018
	No	938	57	734	46	
Inhaled corticosteroid	Yes	20	3	33	5	RR 2.22 (1.04 to 4.74) p=0.038
	No	1058	65	847	54	
Oral corticosteroid	Yes	66	4	51	4	RR 1.39 (0.70 to 2.24) p=0.318
	No	1042	33	883	56	
Bronchiolitis	0	950	61	772	52	OR 1.29 (0.73 to 2.31) p=0.376
	1	105	7	97	7	
	≥2	43	2	23	2	
Pneumonia	0	1085	67	871	60	OR 2.10 (0.73 to 6.03) p=0.169
	≥1	15	3	25	1	
Cold or influenza	0	25	0	19	2	OR 1.04 (0.89 to 1.21) p=0.658
	1–3	539	35	501	30	
	4–9	391	26	291	21	
	≥10	147	9	85	8	
Otitis media	0	856	55	650	38	OR 1.26 (0.83 to 1.91) p=0.277
	1	193	12	167	17	
	≥2	52	2	67	5	

Adjusted relative risks (RR) and 95% CI were estimated for binary outcomes using log binomial regression. Adjusted OR and 95% CI were estimated for ordered grouped counts using ordinal logistic regression. Models were adjusted for: the mother’s level of education; daycare attendance; breast feeding beyond 6 months; siblings at home; environmental tobacco smoke exposure; child’s bedroom flooring (as a surrogate of house dust mite); animal exposure; road traffic density (traffic pollution) around child’s home (little/moderate/dense); and solid fuel pollution within home.

and not always confirmed by a physician. Carer focus group feedback was obtained to ensure questionnaire definitions were unambiguous and to limit misclassification error with only 1.4% of carers reporting difficulty in understanding the study questionnaires. Guidance to clarify the definition of damp was not included within the questionnaires representing another potential cause of misclassification bias. Future studies could address this by using trained inspectors to visit homes to classify and assess the extent of damp. Alternatively, detection and quantification of mould in indoor air and settled dust is possible using Mould Specific Quantitative PCR.¹¹ This technology has been used to develop the Environmental Relative Moldiness Index (ERMI) scale which via dust sampling protocols can quantify the burden of mould within the

home.¹² Children with high ERMI exposure in the first year of life have been shown to have a significantly increased risk of developing asthma at 7 years of age.¹³

Correction for multiple comparisons was not undertaken to avoid inflating type II error so reducing the risk of missing potentially important true associations.^{14 15}

CONCLUSION

Our study highlights the importance of identifying both the presence and location of household damp exposure in the history of a child presenting with recurrent respiratory symptoms. The presence of damp within a child's bedroom should be considered as an eligibility criterion to prioritise households requiring urgent damp assessment and remedial intervention.

Contributors TR: Writing—original draft; formal analysis; data curation; methodology; investigation; writing—review and editing; software; resources; guarantor. SKI: Data curation; writing—original draft; writing—review and editing; project administration. AM: Conceptualisation; funding acquisition; writing—review and editing; writing—original draft. PS: Conceptualisation; writing—original draft; funding acquisition; writing—review and editing. KB: Data curation; writing—original draft; writing—review and editing. SAB: Formal analysis; writing—original draft; writing—review and editing. HR: Conceptualisation; funding acquisition; writing—review and editing; writing—original draft. SM: Conceptualisation; visualisation; writing—original draft; writing—review and editing; supervision; investigation; methodology; validation; funding acquisition; resources. KJF: Conceptualisation; investigation; funding acquisition; writing—original draft; methodology; validation; visualisation; writing—review and editing; supervision; resources.

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ARTIGO ORIGINAL

Impacto indireto da vacina pneumocócica conjugada 13-valente infantil (VPC13) em idosos canadianos: um estudo observacional retrospectivo da Canadian Immunization Research Network (CIRN)

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RESUMO

Contexto A vacina pneumocócica conjugada 13-valente (VPC13) faz parte dos programas de imunização infantil com financiamento público no Ontário e na British Columbia (BC) desde 2010. Avaliámos o impacto indireto dos programas infantis de VPC13 na doença pneumocócica invasiva (DPI) e na hospitalização por pneumonia por todas as causas em adultos mais velhos (com idade ≥65 anos) utilizando um estudo observacional retrospectivo.

Métodos Extraímos casos mensais de DPI e pneumonia por todas as causas de bases de dados de laboratórios e de administrações de saúde entre janeiro de 2005 e dezembro de 2018. Usando um desenho quase experimental de diferença-nas-diferenças, calculámos o rácio de rácios de risco (RRR) usando taxas de incidência de casos de DPI ou pneumonia por todas as causas antes (período pré-VCP13) e depois (período VCP13) de 2010 com taxas de fraturas como controlos.

Resultados As taxas de todas as DPI ou DPI específicas do serotipo da VPC para adultos mais velhos em Ontário e na BC não se alteraram nos 8 anos após a implementação do programa infantil da VPC13. A pneumonia por todas as causas aumentou no Ontário (RRR 1,38, 95% CI 1,11 a 1,71), mas manteve-se inalterada na BC.

Conclusões A proteção comunitária indireta dos adultos mais velhos contra a hospitalização por doença pneumocócica estagnou apesar da maturação dos programas de vacinação infantil VPC13 em duas províncias canadianas.

INTRODUCTION

Adults aged ≥65 years are more susceptible to severe outcomes from infectious diseases because of immunosenescence and chronic comorbidities, such as chronic obstructive pulmonary disease, asthma, diabetes and chronic heart disease. This also includes an increase in the risk of pneumococcal disease and its more severe outcomes, invasive pneumococcal disease (IPD) such as bacteraemia, meningitis and bacteraemic pneumonia.^{1,2} Nasopharyngeal carriage plays a key role in pneumococcal disease causation and transmission, with children being the major reservoir of *Streptococcus pneumoniae*.^{3,4} Routine vaccination of infants and young children with pneumococcal conjugate vaccines (PCVs) has led to community protection with significant decreases in nasopharyngeal carriage rates, hospitalised pneumonia and IPD in several high-income and low-income countries, for all age groups including older adults.^{5–8} In a meta-analysis of indirect effects of childhood PCV programmes on IPD for older adults, maturation of a childhood 13-valent PCV (PCV13) programme was predicted to result in a 50% and 90% reduction in IPD caused by the additional serotypes in PCV13 approximately 4 years and 10 years, respectively, after vaccine introduction.⁸ Publicly funded childhood PCV

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Older adults have benefited from community protection provided by childhood 7-valent pneumococcal conjugate vaccine (PCV7) programmes, reducing severe outcomes such as hospitalisation for pneumonia.
- Invasive pneumococcal disease (IPD) incidence in older adults decreased in Ontario but increased in British Columbia (BC) after PCV13 replaced earlier conjugated vaccines in the routine childhood programme.
- It remains unknown if after maturation, childhood PCV13 vaccination programmes benefited older adults in reducing IPD and all-cause pneumonia hospitalisation in Ontario and BC.

WHAT THIS STUDY ADDS

- Using 8 years of continuous data and a quasi-experimental difference-in-differences design, this study quantified the population-level indirect benefit of community protection of publicly funded childhood PCV13 programme on pneumococcal disease burden in older adults.
- This study found that 8 years of paediatric PCV13 programmes in Ontario and BC did not reduce incidence rates of pneumococcal disease (IPD or all-cause pneumonia) in the older populations in either province.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study highlights the importance of ongoing surveillance to monitor serotypes in the Canadian population to aid evidence-based decision-making and the need for an improved approach to the prevention of IPD in older adults given the low uptake of 23-valent pneumococcal polysaccharide vaccine and the potential benefit of higher-valency PCVs recently made available in Canada.

programmes with successively higher-valency PCVs, PCV7, PCV10 and PCV13, have been in



use in Canada for almost two decades. However, IPD rates have not been consistently declining. A study from Ontario reported substantial declines in pneumonia hospitalisations in older adults, but this study assessed the impact of PCV13 only 3 years after its introduction before the programme had matured.⁹

In our previous study covering two provinces in Canada, we observed a decreased incidence of IPD caused by serotypes covered by PCV7, but the incidence caused by serotypes unique to 23-valent pneumococcal polysaccharide vaccine (PPV23) (ie, serotypes not present in PCV13) and non-vaccine serotypes increased in older adults in both provinces during 2007–2018.¹⁰ We also observed a decrease in the incidence of outpatient and inpatient all-cause community-acquired pneumonia during the PCV13 period in Ontario and British Columbia (BC) in older adults.¹¹

The benefit of mature PCV13 childhood vaccination programmes on community protection for older adults in a Canadian context is unknown. In this study, we examined the impact of paediatric PCV13 vaccination programmes on IPD and all-cause pneumonia in older adults in two large Canadian provinces.

METHODS

Study population, setting and design

We conducted a population-based retrospective observational study in Ontario and BC between 2005 and 2018 to estimate the indirect impact of 8 years of childhood PCV13 programmes on IPD and hospitalised pneumonia in adults aged ≥ 65 years. Ontario is the largest province with approximately 15 million population, whereas BC is the third largest province with a population of approximately 5 million. These two provinces with high-quality data represent different regions of the country and comprise 53% of the Canadian population.

There is no established standard for defining the maturation of pneumococcal vaccination programmes, but we defined the programmes in Canada as mature based on previous studies.¹² The PCV programmes were publicly funded in Ontario and BC at somewhat different times.¹³ In BC, PCV7 was introduced in September 2003 and replaced by PCV13 in June 2010, whereas in Ontario, PCV7 was introduced in January 2005, and it was replaced by PCV10 in October 2009, and then PCV10 was replaced by PCV13 in November 2010. Publicly funded PCV13 has been available to immunocompromised adults aged ≥ 50 years in Ontario since December 2014¹⁴ and to adults with a stem cell transplant (February 2013) or HIV infection (March 2015) in BC.¹⁵ Publicly funded PPV23 has been available for adults aged ≥ 65 years since 1996 in Ontario and 1998 in BC; however, PPV23 uptake remains low (48% for males and 60% for females in 2021).¹⁶

We employed a quasi-experimental difference-in-differences (DID) study design that can be used to estimate potential causal effects of an intervention on observed outcomes in settings where randomised controlled trials are infeasible.^{17,18}

Data sources

We obtained data on laboratory-confirmed IPD, including IPD serotype, from Ontario's integrated Public Health Information System and the BC Centre for Disease Control Public Health Laboratory data. Hospitalisations for all-cause pneumonia and two negative control outcomes, fractures and skin and soft tissue infections (SSTIs), were identified from the Canadian Institute for Health Information's Discharge Abstract Database (DAD).¹⁹ Information on age and sex were obtained from the Registered Persons Database in Ontario and the Medical Services Plan Registration and Premium Billing patient registry in BC.²⁰ Data were analysed separately in Ontario and BC using similar methods. Datasets were linked using unique identifiers; Ontario datasets were analysed at ICES, and BC datasets were analysed at Population Data BC.

Outcomes

A laboratory-confirmed IPD case was defined as isolation of *S. pneumoniae* and/or identification of *S. pneumoniae* DNA from a normally sterile site (eg, blood, cerebrospinal fluid, synovial or peritoneal fluid and bone), excluding the middle ear.^{21,22} IPD cases

with serotype information were grouped into four categories based on serotypes covered by PCVs: (1) PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F), (2) additional PCV13 (serotypes not present in PCV7: 1, 3, 5, 6A, 7F and 19A), (3) unique PPV23 (11 serotypes not present in PCV13: 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F) and (4) non-vaccine (serotypes not included in PCV13 or PPV23).

We used fractures and SSTIs as negative control outcomes because pneumococcal vaccination is not expected to impact or be causally related to these outcomes; these outcomes capture secular, but still distinct, trends in healthcare system use during the study period.

Cases of all-cause pneumonia, fractures and SSTIs assigned as the primary or secondary diagnosis were identified using diagnostic codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA)²³ in DAD (online supplemental table S1). We included all-cause pneumonia hospitalisation without a concurrent IPD diagnosis (ie, included non-invasive pneumonia).

Concurrent IPD diagnoses were identified using the following: pneumococcal meningitis (ICD-10-CA: G00.1), pneumococcal septicaemia (ICD-10-CA: A40.3), pneumococcus elsewhere (eg, infective pericarditis, acute peritonitis, puerperal sepsis and congenital pneumonia) (ICD-10-CA: B95.3) or pneumococcal arthritis and polyarthritis (ICD-10-CA: M00.1). We included fractures and SSTIs without concurrent pneumonia or IPD.

We removed duplicate records using unique identifiers and the admission date in hospitalised patients (ie, DAD database). To identify recurrent cases, we used the discharge date (DAD) to account for the length of hospital stay. We considered IPD and SSTI episodes >30 days and all-cause pneumonia episodes >90 days to be separate episodes and included them. For fracture, we included the first diagnosis.

Statistical analysis

The study period was divided into two intervals: (1) pre-PCV13 period and (2) PCV13 period. Age was categorised into the following groups: ≥ 65 years, 65–74 years, 75–84 years and ≥ 85 years. For each age group, we estimated annual and period-specific incidence rates of IPD, all-cause pneumonia, fractures and SSTIs using Poisson regression models, with population estimates from Statistics Canada as the offset parameter.²⁴

For the indirect effect evaluation using the DID method, we used fractures and SSTIs as controls for primary and secondary analyses, respectively. We visually inspected the annual incidence rates for all identified cases to check that the parallel trend assumption for IPD, pneumonia, fractures and SSTIs during the pre-PCV13 period was not violated. The trends were parallel, except in 2007 due to an outbreak of serotype 5 IPD among socioeconomically disadvantaged populations in BC^{25,26} (online supplemental figure 1). Thus, the change in the incidence of fractures or SSTIs from the pre-PCV13 period to the PCV13 period was assumed to be a valid counterfactual for the change that would have occurred in the incidence of IPD and all-cause pneumonia in the absence of a publicly funded childhood PCV13 immunisation programme.

In Ontario, we employed propensity score matching with the DID method to select controls with similar characteristics in order to make the common trend assumption more plausible. Propensity scores were computed using logistic regression models using age group, sex, comorbidity using the Charlson comorbidity score, month and year. We used the Greedy method to match three controls for each IPD and two controls for each all-cause pneumonia with a standard deviation of less than 20% in absolute value. We tested the parallel trend assumption in the propensity score matched sample using general linear model regressions with the rate of the outcome as the dependent variable, case/control status and time since PCV13 as independent variables and an interaction between case/control status and time since PCV13. A statistically non-significant coefficient for the interaction term suggested that the parallel trend assumption was held. In BC, we matched three controls for each case by age group, sex, month and year.

We estimated the indirect effect as the ratio of risk ratios (RRRs) (ie, the ratio of 'PCV13 risk ratio' and 'pre-PCV13 risk ratio')

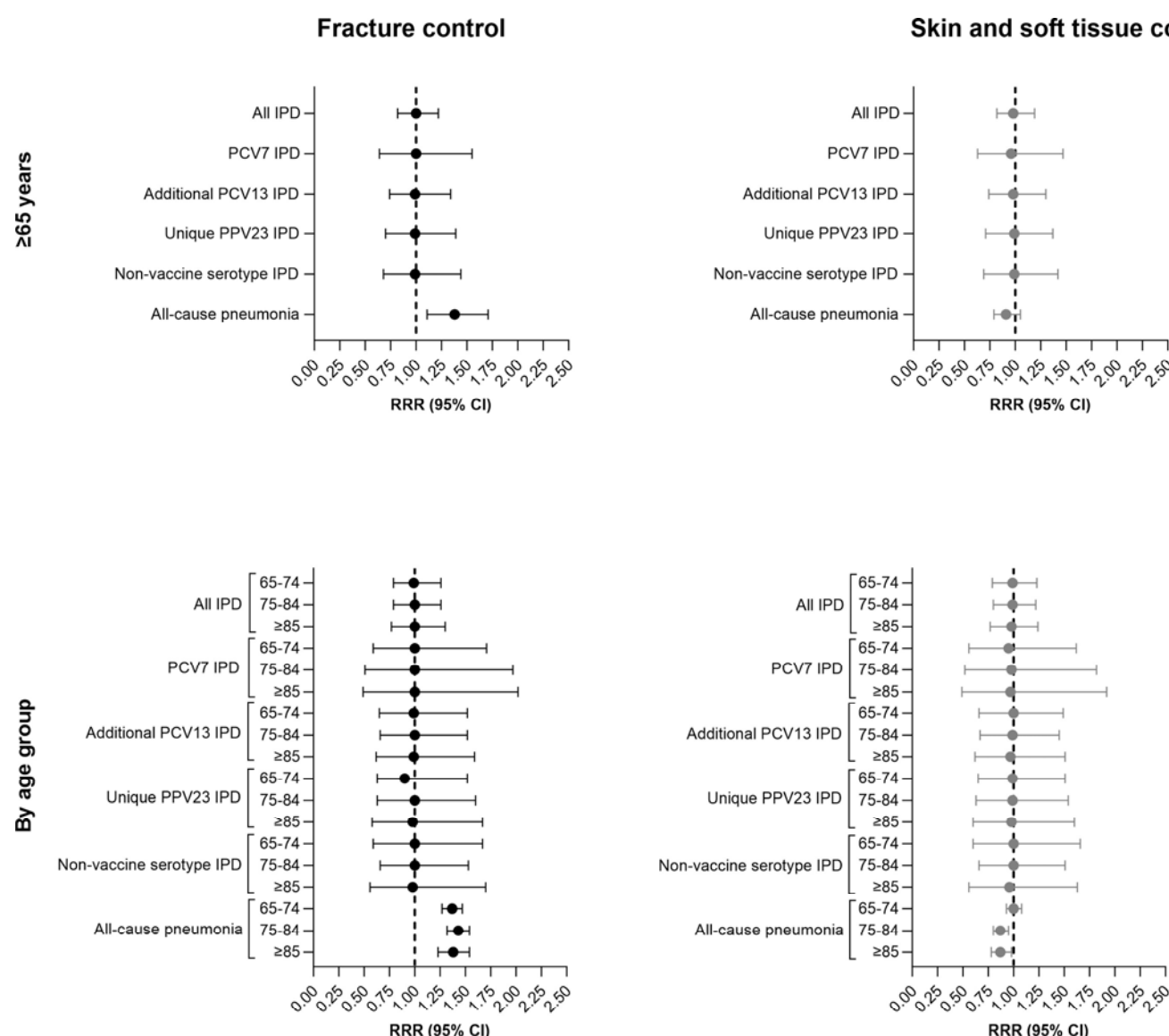


Figure 1 Indirect impact of 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and all-cause pneumonia in older adults aged ≥ 65 years in Ontario, 2005–2018. IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; RRR, ratio of risk ratio.

to determine whether IPD and all-cause pneumonia incidence increased or decreased for older adults after PCV13 introduction into the childhood immunisation programme compared with the pre-PCV13 period. 'PCV13 risk ratio' was calculated from the ratio of the cumulative incidences of either IPD or all-cause pneumonia and either fractures or SSTIs during the PCV13 period; 'pre-PCV13 risk ratio' was calculated from the ratio of the cumulative incidences of IPD or all-cause pneumonia and fractures or SSTIs during the pre-PCV13 period. We analysed monthly incidence data from January 2005 to December 2018 for each disease outcome, with the number of IPD, all-cause pneumonia, fracture and SSTI outcomes for those aged ≥ 65 years overall and by age group using Poisson regression models with the log link function and population as the offset. Monthly serotype group-specific IPD incidence was available from January 2005 to December 2018 in BC and only from January 2007 to December 2018 in Ontario. In Ontario, using the propensity score matched DID analysis, we accounted for the PCV10 programme by incorporating PCV10 fixed effects in the regression models by including a separate binary variable; we also accounted for publicly funded PCV13 for immunocompromised adults aged ≥ 50 years since December 2014 by including a separate binary variable. All analyses were conducted using SAS V.9.4 (SAS Institute) software. All tests were two sided and used $p < 0.05$ as the level of statistical significance.

RESULTS

The total number of identified cases and the calculated mean age-specific incidence rates for IPD, all-cause pneumonia and the two control groups in each of the provinces are shown in table 1. We identified a total of 6575 IPD, 132 023 all-cause pneumonia, 268 468 fracture and 103 405 SSTI cases in Ontario during 2005–2018 with mean annual incidence rates per 100 000 population of 23.9 for IPD, 479.2 for all-cause pneumonia, 974.4 for fracture and 375.3 for SSTI. In BC, we identified a total of 1710 IPD, 35 513 all-cause pneumonia, 91 852 fracture and 19 812 SSTI cases, with mean annual incidence rates per 100 000 population of 16.9 for IPD, 350.5 for all-cause pneumonia, 906.5 for fracture and 195.5 for SSTI. Annual incidence by age group is shown in online supplemental figure 1 and online supplemental table S2.

Serotype information were available for 4591 IPD (79% out of 5812) cases during 2007–2018 in Ontario, with a mean annual incidence per 100 000 population of 1.5 for PCV7 IPD, 5.7 for additional PCV13 IPD, 5.6 for unique PPV23 IPD and 6.0 for non-vaccine serotype IPD among adults aged ≥ 65 years (online supplemental figure 2, table 2, online supplemental table S3). In BC, serotype information were available for 1686 IPD (99% of 1710) cases during 2005–2018; the mean annual incidence per 100 000 population of IPD according to vaccine serotype was 2.1 for PCV7 IPD, 4.7 for additional PCV13 IPD, 5.4 for unique PPV23 IPD and

Table 1 Total counts and mean age-specific annual incidence of invasive pneumococcal disease identified from public health laboratory data, and all-cause pneumonia, fractures and skin and soft tissue infections from health administrative data in adults aged ≥ 65 years in Ontario and British Columbia, Canada, 2005–2018

Age group, years	Invasive pneumococcal disease		All-cause pneumonia		Fracture		Skin and soft tissue infection	
	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)
Ontario								
65–74	2669	17.7 (16.8 to 18.8)	39 262	261.0 (249.8 to 272.7)	64 599	429.4 (417.5 to 441.7)	36 113	240.1 (235.5 to 244.7)
75–84	2244	25.0 (23.5 to 26.6)	50 893	567.5 (546.2 to 589.7)	101 826	1135.5 (1110.3 to 1161.3)	39 048	435.5 (427.5 to 443.6)
≥ 85	1662	46.9 (43.7 to 50.4)	41 868	1181.7 (1132.7 to 1232.7)	102 043	2880.0 (2816.0 to 2945.4)	28 244	797.1 (780.0 to 814.7)
Overall (≥ 65)	6575	23.9 (22.9 to 24.9)	132 023	479.2 (458.9 to 500.3)	268 468	974.4 (929.0 to 1021.9)	103 405	375.3 (364.0 to 387.0)
British Columbia								
65–74	760	13.6 (12.1 to 15.2)	11 441	204.1 (193.4 to 215.5)	24 846	443.3 (412.3 to 476.7)	7305	130.3 (122.9 to 138.2)
75–84	554	17.3 (15.6 to 19.1)	13 684	427.1 (401.8 to 454.1)	32 686	1020.2 (945.2 to 1101.3)	7209	225.0 (209.0 to 242.3)
≥ 85	396	29.9 (26.5 to 33.7)	10 388	784.2 (738.5 to 832.8)	34 320	2591.0 (2417.8 to 2776.6)	5298	400.0 (360.8 to 443.5)
Overall (≥ 65)	1710	16.9 (15.6 to 18.3)	35 513	350.5 (330.3 to 371.9)	91 852	906.5 (838.2 to 980.3)	19 812	195.5 (182.1 to 210.0)

4.5 for non-vaccine serotype IPD among adults aged ≥ 65 years (table 2).

Indirect effect of childhood PCV13 immunisation on IPD and all-cause pneumonia

Ontario

The propensity score matched DID analytic sample for all IPD included 5811 IPD and 17 416 matched fracture controls and 5783 IPD matched with 17 244 SSTI controls. For all-cause pneumonia, the sample included 129 791 all-cause pneumonia and 261 273 matched fracture controls and 106 652 all-cause pneumonia matched with 103 354 SSTI controls. Tests for parallel trend assumption suggested that during the pre-PCV13 period, the parallel trend assumption was not violated using both control conditions, except for the additional PCV13 IPD and SSTI control (data not shown).

In the primary analysis, using fracture as the control condition, we did not observe any statistically significant changes in trends of all IPD or serotype-specific IPD in Ontario for adults aged ≥ 65 years (figure 1, table 3, online supplemental table S4). Similar findings were observed in the secondary analysis using SSTI as the control condition. For all-cause pneumonia, we observed a statistically significant increase in all-cause pneumonia incidence in adults aged ≥ 65 years and across all age groups with fracture used as controls; however, a statistically significant decrease in all-cause pneumonia was observed in adults aged ≥ 75 years using SSTI controls. The effect estimates (RRRs) with and without (data not shown) accounting for publicly funded PCV13 for immunocompromised adults aged ≥ 50 years and the brief PCV10 programme were similar.

British Columbia

The age group and sex matched DID analytic sample for all IPD included 1677 IPD and 5031 matched fracture controls and 1676 IPD matched with 5026 SSTI controls. For all-cause pneumonia, the sample included 32 408 all-cause pneumonia and 97 251 matched fracture controls and 32 402 all-cause pneumonia matched with 97 158 SSTI controls.

In the primary analysis, using fracture as the control condition, we did not observe any statistically significant changes in trends of all IPD, serotype-specific IPD or all-cause pneumonia incidence after PCV13 programme implementation in adults aged ≥ 65 years (figure 2, table 3, online supplemental table S5). Similar findings

were observed in the secondary analysis using SSTI as the control condition.

DISCUSSION

We analysed 8 years of data on cases of IPD and all-cause pneumonia requiring hospitalisation representative of two large Canadian provinces before and after the integration of PCV13 into routine childhood vaccination programme. We showed that publicly funded mature childhood PCV13 immunisation programme (2+1 schedule) in Ontario and BC did not reduce IPD or all-cause pneumonia hospitalisation among older adults in either province. Rates of all-cause pneumonia increased in Ontario in all older adult age groups. These findings collectively suggest that the indirect benefits of childhood PCV vaccination programmes in older adults may have been attenuated by a lower impact of community immunity for strains in PCV13 and not in PCV7 and by a failure of adult PPV23 programmes to reduce the incidence of PPV23 strains (which might be due to either or both of the limited uptake of PPV23 in older adults or waning of protection from PPV23 in these populations).

Indirect effects of PCV on older populations depend on high PCV coverage among children and the longer duration of PCV programme implementation.⁷ A previous study predicted that 90% reduction in IPD caused by PCV7 serotypes in adults aged ≥ 65 years could be achieved in an average of 8.9 (credible interval 7.9–10.3) years following the introduction of PCV7 vaccination.⁸ Modelling predicted a 90% reduction in the additional PCV13 serotype IPD in older adults in an average of 10.3 (credible interval 6.4–20.7) years from the time when PCV7 was replaced by PCV13.⁸ However, neither Ontario nor BC had the PCV13 programme for this duration during our study period to experience discernible level of reduction. In addition, up-to-date relevant PCV (PCV7, PCV10 and PCV13) vaccine coverage in children (ie, valid doses according to the vaccine schedule for age) aged 7 years was lower in Ontario, 74%–80% during 2014–2018,²⁷ than the up-to-date PCV7 or PCV13 vaccine coverage in 2-year-olds in BC, 82%–86% during 2011–2018.²⁸ These may explain the observed lack of indirect effect against IPD in both provinces.

Because pneumococcal vaccines target only some of the more than 100 pneumococcal serotypes, concerns have been raised that non-vaccine serotypes could increase in prevalence and reduce the benefits of vaccination. Nationally, among Canadian older adults

Table 2 Total counts and mean age-specific annual incidence of invasive pneumococcal disease identified from public health laboratory data according to vaccine serotype group in older adults in Ontario and British Columbia, Canada, 2005–2018

Age group, years	PCV7 IPD		Additional PCV13 IPD		Unique PPV23 IPD		Non-vaccine serotype IPD	
	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)	No.	Incidence/100 000 population (95% CI)
Ontario (2007–2018)								
65–74	160	1.2 (1.0 to 1.4)	595	4.5 (4.0 to 5.0)	576	4.3 (3.9 to 4.8)	552	4.2 (3.7 to 4.6)
75–84	112	1.4 (1.2 to 1.7)	468	6.0 (5.3 to 6.7)	454	5.8 (5.2 to 6.5)	511	6.6 (5.9 to 7.3)
≥85	99	3.1 (2.6 to 3.8)	329	10.4 (9.0 to 11.9)	338	10.6 (9.4 to 12.1)	397	12.5 (11.1 to 14.2)
Overall (≥65)	371	1.5 (1.4 to 1.7)	1392	5.7 (5.3 to 6.2)	1368	5.6 (5.3 to 6.0)	1460	6.0 (5.6 to 6.5)
British Columbia (2005–2018)								
65–74	101	1.8 (1.3 to 2.6)	220	3.9 (3.3 to 4.7)	253	4.5 (3.8 to 5.3)	176	3.1 (2.4 to 4.1)
75–84	69	2.2 (1.4 to 3.2)	149	4.7 (4.1 to 5.3)	187	5.8 (4.5 to 7.5)	144	4.5 (3.2 to 6.3)
≥85	41	3.1 (1.9 to 5.1)	103	7.8 (5.8 to 10.5)	107	8.1 (6.5 to 10.1)	136	10.3 (8.1 to 13.0)
Overall (≥65)	211	2.1 (1.5 to 2.9)	472	4.7 (4.1 to 5.3)	547	5.4 (4.6 to 6.3)	456	4.5 (3.5 to 5.8)

IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

during 2011–2015, additional PCV13 serotypes 3, 7F and 19A and unique PPV23 serotype 22F were prevalent vaccine-preventable serotypes with an increase in serotype 3, while serotypes 15A and 23A were prevalent non-vaccine-preventable serotype IPD.¹³ We observed no change in the incidence of IPD in older adults in Ontario and BC. This is not surprising in the context of low PPV23 vaccine uptake in Canadian older adults¹⁶; the lower vaccine effectiveness against IPD, pneumococcal pneumonia and all-cause pneumonia with increasing age; and waning of protection over time in older adults.²⁹ Contrary to our findings, increases in IPD caused by non-PCV13 serotypes in older adults have been reported in the UK, European countries and the USA.^{8,30–34} Partial replacement by non-vaccine serotypes and increases in unique PPV23 serotype IPD have been observed in other high-income countries.^{35,36}

All-cause pneumonia incidence appears to have increased during the PCV13 period in Ontario, which may have resulted from increases in pneumonia caused by PCV13 serotypes 3, 6A and 19A and PPV23 serotypes,³⁷ as well as from increases in pneumonia caused by other bacterial and non-bacterial pathogens, ageing of the population and increased prevalence of comorbidities.

The strength of this study is that the multijurisdictional analysis allowed us to evaluate the entire population of adults aged ≥65 years in Ontario and BC. We were able to examine the indirect impact of PCV13 vaccine on IPD, PCV serotype-specific IPD and hospitalised all-cause pneumonia in older adults up to more than 8 years since the implementation of the paediatric PCV13 vaccine programme in Ontario and BC.

Our retrospective observational study has some limitations. The lack of validation of diagnostic codes in administrative data may have biased our impact estimates. However, we used diagnostic codes used in previous studies evaluating the impact of PCVs.^{9,38} The lack of individual-level pneumococcal vaccination data precluded us from accounting for PCV13 and PPV23 vaccination status in older adults and removing any direct effects imparted by these vaccines. Nationally, the reported uptake of pneumococcal vaccine in adults aged ≥65 years was around 40% from 2006 to 2016 and was 58% during 2018–2019.³⁹ However, with higher vaccine coverage among children, the assumption is that we would be measuring the indirect impact more than the direct impact of adult vaccination programmes. We accounted for publicly funded PCV13 for

Table 3 Indirect impact of PCV13 on invasive pneumococcal disease and all-cause pneumonia in older adults aged ≥65 years in Ontario and British Columbia, 2005–2018*

Outcome	Fracture control				Skin and soft tissue infection control			
	Incidence per 100 000				Incidence per 100 000			
	Case, pre-PCV13, PCV13	Control, pre-PCV13, PCV13	Ratio of risk ratios (95% CI)	P value	Case, pre-PCV13, PCV13	Control, pre-PCV13, PCV13	Ratio of risk ratios (95% CI)	P value
Ontario								
All IPD	21.2, 22.2	63.3, 66.7	1.00 (0.82 to 1.22)	0.9794	21.0, 21.7	62.0, 65.1	0.98 (0.82 to 1.19)	0.8642
PCV7 IPD	2.6, 0.9	7.9, 2.6	1.00 (0.64 to 1.55)	1.0000	2.6, 0.8	7.6, 2.5	0.96 (0.63 to 1.47)	0.8644
Additional PCV13 IPD	4.7, 5.8	14.1, 17.4	0.99 (0.74 to 1.34)	0.9729	4.7, 5.5	13.9, 16.6	0.98 (0.74 to 1.30)	0.9144
Unique PPV23 IPD	2.6, 5.0	7.8, 15.1	0.99 (0.70 to 1.39)	0.9403	2.7, 4.9	7.9, 14.8	0.99 (0.71 to 1.37)	0.9371
Non-vaccine serotype IPD	2.5, 5.9	7.5, 17.7	0.99 (0.68 to 1.44)	0.9666	2.5, 5.9	7.4, 17.8	0.99 (0.69 to 1.42)	0.9508
All-cause pneumonia	391.6, 507.9	974.9, 918.4	1.38 (1.11 to 1.71)	0.0041	376.9, 366.8	344.1, 366.8	0.91 (0.79 to 1.05)	0.2156
British Columbia								
All IPD	15.4, 17.1	46.3, 51.2	1.00 (0.83 to 1.20)	0.9794	15.4, 17.1	46.1, 51.2	1.00 (0.83 to 1.19)	0.9678
PCV7 IPD	3.5, 1.4	10.5, 4.1	0.99 (0.67 to 1.45)	0.9476	3.5, 1.4	10.6, 4.1	1.00 (0.68 to 1.47)	0.9882
Additional PCV13 IPD	4.9, 4.5	14.8, 13.5	1.00 (0.76 to 1.31)	1.00	4.9, 4.5	14.7, 13.5	0.99 (0.76 to 1.30)	0.9635
Unique PPV23 IPD	4.3, 5.8	12.9, 17.5	1.00 (0.76 to 1.32)	1.00	4.3, 5.8	12.9, 17.5	1.00 (0.76 to 1.31)	0.9863
Non-vaccine serotype IPD	2.3, 5.4	6.8, 16.3	1.00 (0.72 to 1.39)	1.00	2.3, 5.4	6.8, 16.3	1.00 (0.72 to 1.39)	1.00
All-cause pneumonia	330.0, 315.0	990.2, 945.0	1.00 (0.92 to 1.09)	0.9932	329.4, 315.3	986.6, 945.9	1.00 (0.92 to 1.09)	0.9664

*Invasive pneumococcal disease identified from public health laboratory data and pneumonia identified from health administrative data.
IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

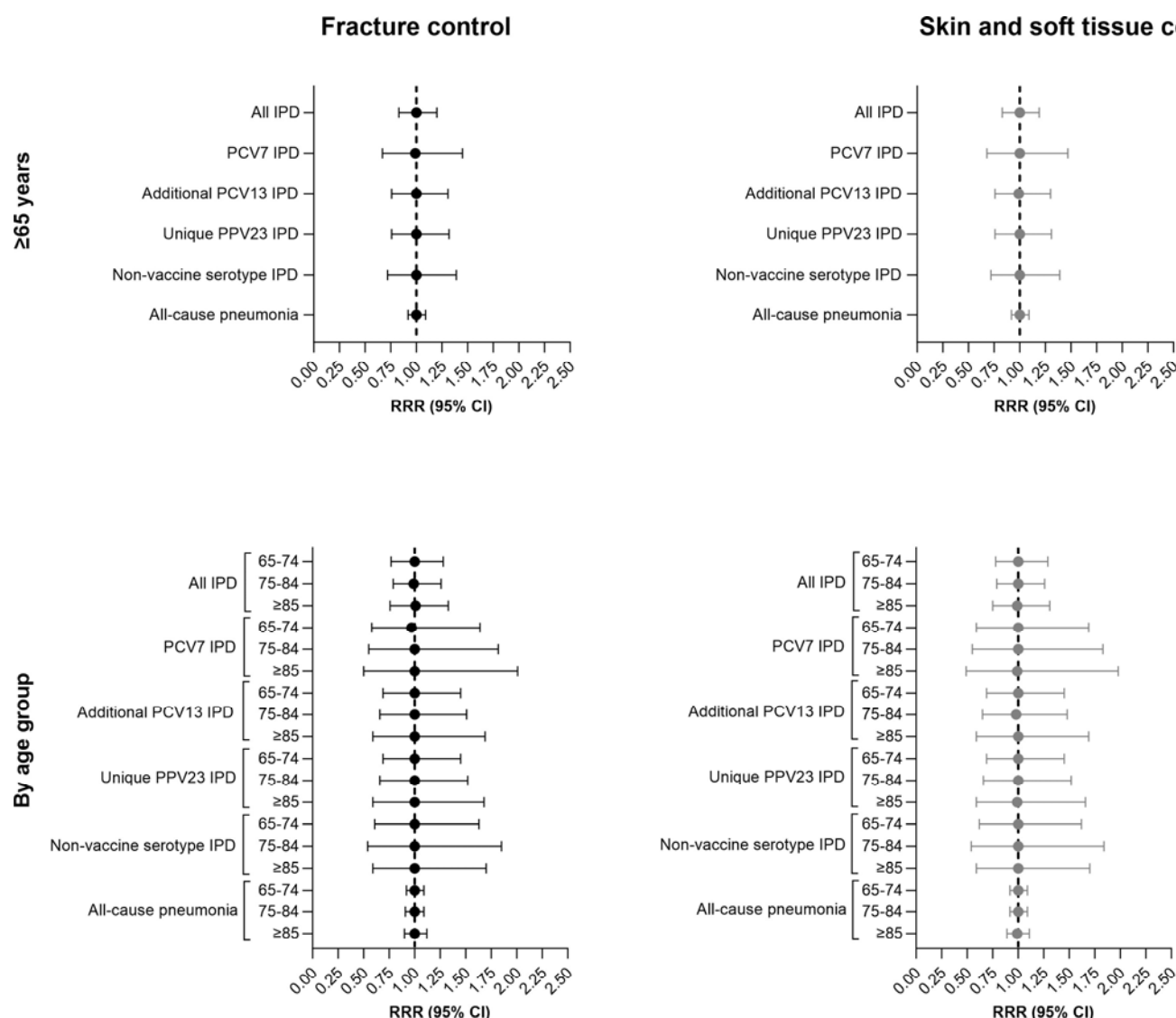


Figure 2 Indirect impact of 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and all-cause pneumonia in older adults aged ≥ 65 years in British Columbia, 2005–2018. IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; RRR, ratio of risk ratio.

immunocompromised adults aged ≥ 50 years in Ontario that was implemented in December 2014. We were unable to account for confounders such as smoking because of a lack of data. We could employ matching only by age group and sex in BC because of a lack of information on comorbidity in the analytic dataset for this study, and there remains the potential for residual confounding. However, in DID analysis, the covariates do not need to be balanced between the intervention and control groups, and only if a covariate differs between the treatment and control groups and if the relationship between the covariate and the outcome varies over time, then that covariate is considered as a confounder in a DID analysis.⁴⁰ Additionally, an absence of selection bias resulting from unobserved characteristics is not testable. The parallel trend assumption was assessed with graphical inspection in BC, and it was assumed that IPD, pneumonia, fracture and SSTI rates trended closely during the pre-PCV13 period. We used monthly counts to model our DID analysis resulting in numerous pre-PCV13 and PCV13 period time points. As such, the parallel trend assumption (unmeasured variables are either time-invariant group attributes or time-varying factors that are group invariant) may not hold across all groups and time points, although it may hold for some groups and time points, and the results should be interpreted with caution.⁴¹ We employed two negative control conditions to account for secular trends in the healthcare system. The impact of PCV13 programme on all-cause pneumonia in Ontario was not comparable between the control conditions suggesting that the SSTI control may not have adequately

captured the secular trends and may have been subject to residual confounding.

In conclusion, we observed limited indirect benefit of childhood PCV13 vaccination on pneumococcal disease burden in Canadian older adults even after 8 years of publicly funded childhood PCV13 vaccination programme implementation. Although publicly funded PPV23 has been available to adults aged ≥ 65 years in Canada since the mid-1990s, its uptake remains low in older adults.¹⁶ Our study would suggest that the decreasing IPD trend has plateaued or reversed and warrants consideration of the potential benefits of immunising older adults with PCV,^{42–44} particularly higher-valency vaccines (PCV15 and PCV20) recently authorised and recommended for pneumococcal programmes in Canada⁴⁵ or newer products in the pipeline (PCV21 and PCV24). Taking into consideration the current evidence on disease burden and the efficacy, effectiveness, immunogenicity, safety and cost-effectiveness of PCV15 and PCV20, Canada's National Advisory Committee on Immunization has recently provided a strong recommendation for PCV20 for older adults, as well as individuals under 65 years of age with specific risk factors.⁴⁵

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Ethics approval This study involves human participants. We obtained ethics approval from the Ethics Review Boards of the Ontario Agency for Health Protection and Promotion (2019-037.01), the University of British Columbia (H19-02806) and BC Ministry of Health. This study used deidentified secondary data compiled and provided by data stewards to the researchers. As such, informed consent was not obtained by the researchers for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data may be obtained from a third party and are not publicly available. The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organisations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors on request, understanding that the computer programs may rely on coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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ARTIGO ORIGINAL

A menopausa precoce e a terapia hormonal como fatores determinantes dos resultados de saúde pulmonar: uma análise secundária usando o estudo PLCO

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RESUMO

Fundamentação A menopausa natural precoce (M precoce; <45 anos de idade) aumenta o risco de morbidade e mortalidade pulmonar em mulheres fumadoras. No entanto, desconhece-se em grande medida se a menopausa precoce devida a cirurgia apresenta efeitos semelhantes e se a terapia hormonal menopáusica (THM) protege das doenças pulmonares.

Objetivos Avaliar as associações de M precoce e THM com morbidades e mortalidades pulmonares, utilizando o estudo prospectivo Prostate, Lung, Colorectal and Ovarian (PLCO).

Métodos Estimamos o risco entre 69 706 mulheres pós-menopáusicas no ensaio PLCO, estratificado por tipos de menopausa e nível de tabagismo.

Resultados A M precoce foi associada a um risco acrescido da maioria das doenças pulmonares e dos resultados de mortalidade em “ever smokers” (ex-fumadoras), sendo que o risco mais elevado observado para mortalidade respiratória (HR 1,98, IC 95% 1,34 a 2,92) pertenceu a quem apresentava ooforectomia bilateral (OB). A M precoce esteve positivamente associada à bronquite crônica e à mortalidade por todas as causas, não oncológica e respiratória em nunca fumadoras com menopausa natural ou OB, sendo o risco mais elevado observado para OB - mortalidade respiratória (HR 1,91, IC 95% 1,16 a 3,12). O uso de THM em algum momento foi associado a redução da mortalidade por todas as causas, não oncológica e cardiovascular em todos os tipos de menopausa, independentemente do nível de tabagismo, e foi adicionalmente associada a redução do risco de cancro não ovárico, cancro do pulmão (CP) e mortalidade respiratória em ex-fumadoras. Entre as fumadoras, o uso de THM em algum momento foi associado a uma redução da HR para a mortalidade por todas as causas, não oncológica e cardiovascular de uma forma dependente da duração.

Conclusões As fumadoras com M precoce devem ser assinaladas para a cessação tabágica e rastreio de CP, independentemente do tipo de menopausa. As utilizadoras de THM apresentaram uma menor probabilidade de morrer devido a CP e de doenças respiratórias em ex-fumadoras.

INTRODUCTION

Natural cessation of menstruation, that is, natural menopause, results from a gradual decline in oestrogen levels driven by ovarian ageing.¹ Menopause can also result from bilateral oophorectomy (BO), with or without hysterectomy, leading to a sudden and complete loss of ovarian oestrogen production. Women receiving a hysterectomy without BO do not lose ovarian function immediately. However, compelling evidence suggests that hysterectomy induces premature ovarian failure due to the lack of uterine blood flow to the ovaries or the lack of uterine secretions to inhibit pituitary follicle-stimulating hormone (FSH) leading to accelerated follicular depletion.^{2–5} The risk for several chronic conditions such as cardiovascular diseases and osteoporosis increases dramatically in postmenopausal women and the loss of circulating oestrogens may be a common cause.⁶ The United States Preventive Services Task Force (USPSTF) and the North American Menopause Society (NAMS) agree on the use of menopausal hormone therapy (MHT)

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Early natural menopause (early-M; <45 years of age) increases the risk of malignant and non-malignant lung morbidities and mortalities in individuals who smoke. However, it is largely unknown whether early-M due to surgery can also cause similar adverse effects. Menopausal hormone therapy (MHT) is recommended to manage perimenopausal symptoms. However, its recommendations for primary prevention of chronic conditions in postmenopausal women are inconsistent.

WHAT THIS STUDY ADDS

► The associations of early-M and MHT with malignant and non-malignant lung morbidities and mortalities are similar to that seen in smokers with natural menopause, with several outcomes demonstrating stronger associations in smokers with bilateral oophorectomy. The associations of early-M with non-malignant respiratory outcomes were also observed in never smokers. In women receiving hysterectomy only, the associations of early-M and MHT were predominantly seen in ever smokers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Our study provides strong evidence implicating early-M, either naturally occurring or induced by surgery, as a risk factor for lung morbidities and mortalities in never and ever smokers during their postmenopausal life. Thus, smokers with early-M should be targeted for smoking cessation and lung cancer (LC) screening regardless of menopause types. Furthermore, among smokers, MHT users had a lower likelihood of dying from LC and respiratory diseases.

opporosis increases dramatically in postmenopausal women and the loss of circulating oestrogens may be a common cause.⁶ The United States Preventive Services Task Force (USPSTF) and the North American Menopause Society (NAMS) agree on the use of menopausal hormone therapy (MHT)

for the management of perimenopausal symptoms, such as hot flashes or vaginal dryness. However, their recommendations differ for primary prevention of chronic conditions like bone loss in postmenopausal individuals. The USPSTF advises against the use of MHT for the primary prevention of chronic conditions, but the NAMS recommends the use of MHT for primary prevention in specific groups of women, for example, under the age of 60 or within 10 years of menopause onset. Additionally, NAMS suggests the continuation of MHT use beyond age 65 based on individual risk–benefit analysis and regular re-evaluation.^{7–9}

Natural menopause commonly occurs in women between 45 and 55 years of age. Early natural menopause (early-M) is generally defined as occurring in those <45 years of age. Age at natural menopause is a multifactorial phenotype that has genetic and non-genetic determinants. Cigarette smoking is an established risk factor for early-M and higher levels of smoking intensity, duration and cumulative dose and earlier age at initiation have been all associated with risk for early-M.¹⁰ Cigarette smoking also shows prolonged and dose-dependent adverse effects (eg, lower blood oestradiol, lower number of retrieved oocytes and embryos and lower implantation and pregnancy rates) on gonadotropin-stimulated ovarian function in women receiving assisted reproductive services.^{11,12} A recent genome-wide association study in over 200K women of European ancestry identified 290 genetic determinants of natural ovarian ageing using age at natural menopause as the proxy, with DNA damage response as the top biological pathway implicated.¹³ Thus, ovarian injury and repair under the chronic insults of toxicants in tobacco smoke¹⁰ may help drive early-M, which represents a biomarker of ovarian ageing among smokers. Cigarette smoking may also lead to early-M through inhibition of aromatase enzyme activity which catalyses the conversion of androgens into oestrogens.¹⁴ BO or hysterectomy are mainly consequences of underlying diseases, for example, ovarian tumour or cyst, endometriosis, or uterine fibroids, or as prophylactic measures to reduce the risk of ovarian, fallopian tube and peritoneal cancers, particularly for women at high risk (eg, BRCA1/BRCA2 mutation carriers).¹⁵ Although surgical menopause is not caused by ovarian ageing, it leads to sudden or accelerated loss of ovarian function.

Mounting evidence supports early-M as a detrimental factor for lung diseases, respiratory exacerbation and all-cause and cardiovascular mortality, and as a protective factor for mortality from breast, ovarian and endometrial cancers.^{16–23} Our recent analyses in moderate and heavy smokers from the Pittsburgh Lung Screening Study (PLUSS) cohort found that early-M was associated with obstructive lung diseases, a more rapid decline of the ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) and higher all-cause, lung cancer (LC) and respiratory mortality.²⁴ Moreover, women with early-M who continued smoking had a >4.5-fold increased risk for LC incidence and cancer-specific mortality compared with those without early-M or who quit smoking.²⁴ Two mechanisms were proposed: (1) early-M is a biomarker of reproductive and somatic ageing due to pan-organ host–environment interactions (no causality) and (2) women with early-M may have shorter lifetime oestrogen exposure that potentially accelerates somatic ageing (causality).²⁴ However, the role of early-M in women with surgical menopause is unclear.

The current study leverages the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial that has a large number of postmenopausal women with detailed menopause-related information, including timing and types of menopause, surgical removal of the uterus and/or ovaries and type and duration of MHT use. Our objectives are as follows: (1) to replicate the associations identified in ever smokers with natural menopause from the PLUS cohort²⁴ and evaluate these associations in never smokers and (2) to assess these associations in never and ever smokers with surgical menopause (BO or hysterectomy with ovarian conservation). Because cigarette smoking was reported to reduce age at natural menopause and was also identified to affect timing of menopause-

related surgery in this study, all analyses were conducted in never and ever smokers separately.

METHODS

Study population

The PLCO Cancer Screening trial is a multicentre randomised controlled trial to determine whether certain screening exams reduce mortality from prostate, lung, colorectal and ovarian cancers.²⁵ Subjects were recruited at 10 centres across the USA between 1993 and 2001. Major enrolment criteria included men and women ages 55–74 years without prior diagnosis of prostate, lung, colorectal or ovarian cancer or recent cancer screening for the organs of interest. Specific efforts were in place to ensure the enrolment of black, Hispanic and Asian minorities, which together consisted of 10.4% of the trial population. Approximately 155 000 participants were enrolled between November 1993 and July 2001 among which 78 209 were female. A total of 8187 women were excluded due to: (1) missing age at menopause (n=2738); (2) menopausal type not in one of the three groups described above (n=4823); (3) unknown cigarette smoking status (n=5) or (4) unknown body mass index (BMI, n=937), as BMI is a risk factor for health outcomes assessed in this study (figure 1). Current analyses include postmenopausal women who reported natural (n=46 025), BO (n=8303) or hysterectomy with ovarian conservation (hereafter noted as hysterectomy only, n=15 378) at study entry. The National Cancer Institute Cancer Data Access System approved data access under request PLCO-981 on 24 June 2022.

Menopause and MHT use history

Types and timing of menopause and MHT use history were based on baseline questionnaires implemented between 1993 and 2001. Early-M was defined as age at menopause <45 years based on question 32—“How old were you when you had your last period?” Menopause type (ie, natural menopause, BO, hysterectomy only) was defined based on question 33—“Did your periods stop because of natural menopause, surgery, radiation, or drug therapy?”, question 47—“Have you had a hysterectomy, that is, have you had your uterus or womb removed?”, question 49—“Have you ever had one or both of your ovaries removed?” and question 50—“What exactly was removed?” Women whose menopause was due to radiation or drug therapy were excluded (figure 1). Among the 46 025 women whose menopause naturally stopped, 1121 women also reported BO and hysterectomy, 1260 reported hysterectomy without BO, and 46 reported BO without hysterectomy at baseline. Excluding those subjects (n=2427) did not change the associations reported. Ever MHT use for menopause symptoms was defined based on question 51—“Sometimes women take female hormones such as oestrogen or progesterone around the time of menopause.

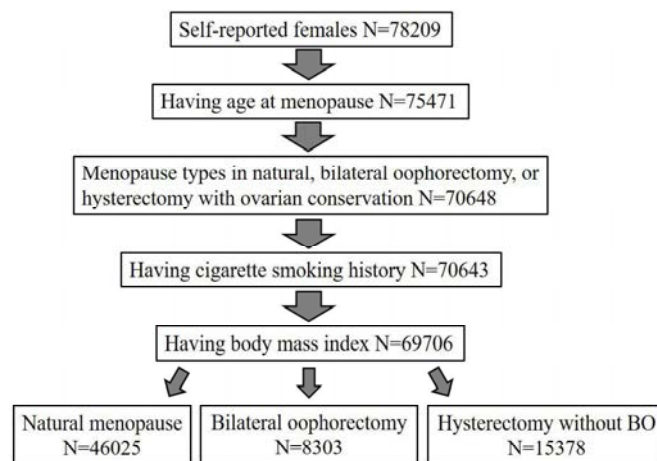


Figure 1 Flow chart of the sample size. Majority of women removed were due to missing age at menopause or menopausal type not in one of the three groups studied, that is, natural menopause, bilateral oophorectomy and hysterectomy only.

Table 1 Association between early menopause (vs non-early menopause) and health outcomes by menopause type and smoking status in women from the PLCO trial*

Outcome	Never smoker			Ever smoker		
	Natural menopause	BO	Hysterectomy only	Natural menopause	BO	Hysterectomy only
Lung disease†						
Emphysema	1.34 (0.78 to 2.31)	Not analysed	Not analysed	1.23 (1.01 to 1.50)‡	1.99 (1.31 to 3.01)§‡	1.29 (0.93 to 1.80)
Chronic bronchitis	1.31 (1.06 to 1.62)‡	1.86 (1.45 to 2.38)§¶	1.29 (1.03 to 1.61)‡	1.09 (0.93 to 1.27)	1.61 (1.24 to 2.07)§¶	1.38 (1.10 to 1.71)‡
Cancer incidence**						
LC	1.09 (0.58 to 2.03)	Not analysed	Not analysed	1.31 (1.08 to 1.58)‡	1.05 (0.70 to 1.57)	1.43 (1.03 to 1.99)‡
Mortality**						
All-cause	1.10 (1.02 to 1.19)‡	1.20 (1.06 to 1.36)‡	1.00 (0.91 to 1.09)	1.26 (1.19 to 1.35)¶	1.27 (1.12 to 1.45)¶	1.28 (1.15 to 1.41)¶
Non-ovarian cancer	0.95 (0.80 to 1.13)	0.94 (0.73 to 1.19)	0.97 (0.80 to 1.18)	1.19 (1.06 to 1.34)‡	1.10 (0.87 to 1.38)	1.15 (0.96 to 1.39)
LC	0.94 (0.51 to 1.75)	Not analysed	Not analysed	1.20 (1.00 to 1.44)‡	1.20 (0.82 to 1.75)	1.41 (1.04 to 1.92)‡
Non-cancer	1.16 (1.06 to 1.26)‡	1.30 (1.13 to 1.50)¶	1.02 (0.92 to 1.13)§	1.32 (1.22 to 1.42)¶	1.35 (1.15 to 1.58)¶	1.35 (1.20 to 1.53)¶
Respiratory	1.51 (1.15 to 2.00)‡	1.91 (1.16 to 3.12)‡	1.11 (0.77 to 1.60)	1.36 (1.15 to 1.62)¶	1.98 (1.34 to 2.92)¶	1.37 (1.03 to 1.83)‡
Cardiovascular	1.05 (0.92 to 1.21)	1.38 (1.11 to 1.72)§‡	0.99 (0.85 to 1.15)	1.31 (1.16 to 1.48)¶	1.19 (0.94 to 1.51)	1.26 (1.05 to 1.51)‡

*Sample size is in online supplemental table 1. Not analysed due to limited power.

†Logistic regressions were performed to assess the associations of self-reported lung health conditions (emphysema and chronic bronchitis) with early menopause types. Covariates adjusted include intervention arm, age at enrolment, race (NHB and other race with NHW as the reference), education status (less than college vs some college or above), height, BMI group (underweight (BMI of ≤ 18.5 kg/m²), overweight (BMI of 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) with normal weight (BMI of 18.5–25 kg/m²) as the reference), baseline pack-years (for ever smokers) and ever MHT use.

‡P for effect estimate of early-M < 0.05 .

§Compared with the effect of early menopause in natural menopause, $p < 0.05$.

¶P for effect estimate of early-M < 0.001 .

**Cox proportional-hazards models were used to estimate the effect of early menopause types on lung cancer (LC) incidence and all-cause and cause-specific (LC, non-cancer, cancer (non-reproductive), respiratory, cardiovascular and reproductive cancer) mortality. Covariates adjusted include intervention arm, age at enrolment, race (NHB and other race with NHW as the reference), education status (less than college vs some college or above), BMI group (underweight (BMI of ≤ 18.5 kg/m²), overweight (BMI of 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) with normal weight (BMI of 18.5–25 kg/m²) as the reference), baseline pack-years (for ever smokers) and ever MHT use.

BMI, body mass index; BO, bilateral oophorectomy; early-M, early menopause; LC, lung cancer; MHT, menopausal hormone therapy; NHB, non-Hispanic Black; NHW, non-Hispanic White; PLCO, Prostate, Lung, Colorectal and Ovarian.

Have you ever used female hormones (tablets, pills or creams) for menopause?” MHT use duration was defined based on question 53—“For how many total years did you take female hormones?”

Type of MHT use was extracted from the supplemental questionnaire (Question 70—What type of hormone replacement therapy (HRT) did you take when you first began HRT?) implemented in a subset of cohort participants between 2006 and 2007. Only about 9.7% of women reporting MHT use at baseline switched to MHT type after an average of 10 years of use, thus we used initial MHT type for data analyses. The majority of MHT changes were between types of pills (55.6%) or from pills to non-pills (34.8%).

Lung comorbidities

Self-reported personal history of emphysema and chronic bronchitis (CB) was collected at baseline using questions of “Had a doctor ever told you that you have emphysema?” and “Had a doctor ever told you that you have CB?”

LC incidence

LC occurrence was identified through chest radiograph and other means including self-reports, family reports, death certificates, etc.²⁵ Information on the date of cancer diagnosis, the International Classification of Diseases for Oncology second edition code (topography in C340, C341, C342, C343, C348, C349 and morphology not in 872x–879x, 905x, 914x, 959x, 965x–974x, 980x, 982x–994x), diagnostic procedures, cancer stage, grade and histopathologic type and initial cancer treatment were obtained. Request PLCO-981 included the release of cancer incidence data reported to 31 December 2009 (median follow-up time 11.3 years) and identified 1306 LC occurrences among the 69 706 women.

Mortality

Mortality data were primarily collected from (1) the administration of the Annual Study Update questionnaires; (2) reports from relatives, friends or physicians and (3) National Death Index Plus

searches.²⁵ Death certificates and medical records were reviewed to determine a single underlying cause of death based on rules established by the National Center for Health Statistics and through a Death Review Process to provide a more accurate assessment of the trial endpoints, that is, PLCO cancers. Respiratory illness includes the International Classification of Diseases ninth revision code range (460–519). Request PLCO-981 included the release of mortality data to 2018 (median follow-up 19.2 years) and identified 21 147 deaths among the 69 706 women.

Statistical analysis

Demographic variables and selected outcomes were summarised by menopause types and early-M status using methods appropriate for the scale (categorical vs continuous) and/or distribution (skewed vs symmetric). Incidence and mortality rates per 100 000 person-years were reported in online supplemental tables 1 and 2. Because cigarette smoking was reported to reduce age at natural menopause and was also identified to affect timing of menopause-related surgery in this study, all analyses were conducted in never and ever smokers separately. Logistic regressions were performed to assess the associations of self-reported lung comorbidities (emphysema and CB) at baseline with early-M status (early vs non-early) and MHT (ever vs never). Cox proportional-hazards models were used to estimate the effect of early-M and MHT on time to LC incidence and time to all-cause and cause-specific (LC, non-cancer, non-ovarian cancer, respiratory and cardiovascular) death. For outcomes with statistically significant associations with MHT use as a binary variable, additional analyses were conducted by treating MHT use as a categorical variable (0, ≤ 1 year, 2–3 years, 4–5 years, 6–9 years and ≥ 10 years). When assessing disease-specific mortality in survival modelling, death from other or unknown causes was censored. Covariates adjusted in the above models included intervention arm, age at enrolment, race/ethnicity (non-Hispanic Black (NHB) and other race with non-Hispanic White (NHW) as the reference), education status (less than

Table 2 Association between ever MHT use (vs never MHT use) and health outcomes by menopause type and smoking status in women from the PLCO trial*

Outcome	Never smoker			Ever smoker		
	Natural menopause	BO	Hysterectomy only	Natural menopause	BO	Hysterectomy only
Lung disease†						
Emphysema	1.10 (0.76 to 1.59)	Not analysed	Not analysed	0.89 (0.77 to 1.04)	0.90 (0.50 to 1.63)	1.00 (0.74 to 1.35)
Chronic bronchitis	1.09 (0.94 to 1.25)	1.14 (0.76 to 1.71)	1.12 (0.90 to 1.40)	1.07 (0.96 to 1.20)	1.70 (1.06 to 2.74)‡§	1.17 (0.96 to 1.43)
Cancer incidence¶						
LC	0.96 (0.65 to 1.40)	Not analysed	Not analysed	0.84 (0.72 to 0.97)§	0.88 (0.46 to 1.67)	0.92 (0.69 to 1.23)
Mortality¶¶						
All-cause	0.91 (0.86 to 0.95)**	0.79 (0.67 to 0.93)§	0.90 (0.82 to 0.98)§	0.84 (0.80 to 0.88)**	0.69 (0.57 to 0.83)**	0.80 (0.73 to 0.88)**
Non-ovarian cancer	0.90 (0.82 to 1.00)§	1.03 (0.71 to 1.50)	0.78 (0.64 to 0.95)§	0.84 (0.77 to 0.92)**	0.78 (0.54 to 1.13)	0.80 (0.68 to 0.95)§
LC	0.90 (0.63 to 1.28)	Not analysed	Not analysed	0.78 (0.68 to 0.89)**	0.59 (0.35 to 1.00)§	0.97 (0.74 to 1.28)
Non-cancer	0.89 (0.85 to 0.95)**	0.73 (0.60 to 0.88)§	0.91 (0.82 to 1.01)	0.83 (0.78 to 0.88)**	0.66 (0.53 to 0.82)**	0.80 (0.71 to 0.89)**
Respiratory	0.99 (0.81 to 1.20)	1.54 (0.69 to 3.44)	0.92 (0.64 to 1.33)	0.78 (0.68 to 0.89)**	0.56 (0.35 to 0.91)§	0.71 (0.55 to 0.92)§
Cardiovascular	0.88 (0.80 to 0.96)§	0.64 (0.48 to 0.84)§	0.90 (0.77 to 1.05)	0.80 (0.73 to 0.88)**	0.52 (0.38 to 0.70)‡**	0.84 (0.71 to 1.00)§

*Sample size is in online supplemental table 2. Not analysed due to limited power.

†Logistic regressions were performed to assess the associations of self-reported lung health conditions (emphysema and chronic bronchitis) with ever MHT use. Covariates adjusted include intervention arm, age at enrolment, race (NHB and other race with NHW as the reference), education status (less than college vs some college or above), height, BMI group (underweight (BMI of ≤ 18.5 kg/m²), overweight (BMI of 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) with normal weight (BMI of 18.5–25 kg/m²) as the reference), baseline pack-years (for ever smokers) and early menopause.

‡Compared with the effect of ever MHT use in natural menopause, $p < 0.05$.

§P for effect estimate of ever MHT < 0.05 .

¶Cox proportional-hazards models were used to estimate the effect of ever MHT use on lung cancer (LC) incidence and all-cause and cause-specific (LC, non-cancer, cancer (non-reproductive), respiratory, cardiovascular and reproductive cancer) mortality. Covariates adjusted include intervention arm, age at enrolment, race (NHB and other race with NHW as the reference), education status (less than college vs some college or above), BMI group (underweight (BMI of ≤ 18.5 kg/m²), overweight (BMI of 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) with normal weight (BMI of 18.5–25 kg/m²) as the reference), baseline pack-years (for ever smokers) and early menopause.

**P for effect estimate of ever MHT < 0.001 .

BMI, body mass index; BO, bilateral oophorectomy; early-M, early menopause; LC, lung cancer; MHT, menopausal hormone therapy; NHB, non-Hispanic Black; NHW, non-Hispanic White; PLCO, Prostate, Lung, Colorectal and Ovarian.

college vs some college or above), BMI group (underweight (≤ 18.5 kg/m²), overweight (25–30 kg/m²) and obese (≥ 30 kg/m²) with normal weight (18.5–25 kg/m²) as the reference) and baseline pack-years (among ever smokers). Height was additionally adjusted in models with emphysema or CB as the outcome.²⁴ Baseline comorbidities were not included in the Cox models to avoid the risk of overadjustment as those variables were assumed to be intermediate variables along the path of early-M or MHT use and mortality. We analysed data by each menopause type separately to assess the association between early-M or MHT and an outcome because natural menopause, BO and hysterectomy only have different underlying causes and/or consequences on circulatory oestrogen levels. We then analysed all menopause type data jointly by including interaction terms between menopause type and early-M, and between menopause type and MHT in regression models to directly assess the differential association of early-M or MHT with an outcome by menopause type. Association analyses were determined based on the findings in female smokers with natural menopause from our previous study using the PLuSS cohort as well as the necessity for extrapolating these findings into women with surgical menopause.²⁴ Health outcomes analysed were somewhat related. Thus, instead of setting arbitrary cut-offs for claiming study-wide significance, we chose to weight evidence based on nominal p values as well as consistency across relevant outcomes and/or menopause types. All statistical analyses were performed using SAS (V.9.4; SAS Institute, Cary, North Carolina, USA).

RESULTS

Participant characteristics

Overall, 20 163 (28.9%) women in the entire sample reported early-M, including 4699 (10.2%) with natural menopause, 3922 (47.2%) with BO and 11 542 (75.1%) with hysterectomy only (online supplemental table 3). Women with early-M were more

likely to have ever smoked, and if smoked, had higher numbers of cigarettes per day, longer smoking duration and higher pack-years compared with those with non-early-M, irrespective of menopause types. Moreover, women with early-M were less likely to have reported a higher education level, at least among those with natural menopause and those with BO.

Associations of early-M with health outcomes

Among ever smokers with natural menopause, early-M was associated with an increased risk of all health outcomes except baseline CB (table 1). Among those with BO, significant associations with early-M were identified for baseline emphysema and CB, and all-cause, non-cancer and respiratory mortality. Moreover, emphysema was associated with an OR of 1.23 (95% CI 1.01 to 1.50) in those with natural menopause but more strongly ($p < 0.05$ for difference in OR between natural menopause and BO) associated in those with BO (OR 1.99, 95% CI 1.31 to 3.01). Among ever smokers with hysterectomy only, statistically significant associations with early-M were identified for an increased risk of CB, LC incidence and all-cause, LC, non-cancer, respiratory and cardiovascular mortality. These results were similar before (online supplemental table 4) and after (table 1) adjustment for covariates.

Among never smokers with natural menopause, early-M (vs non-early-M) was associated with higher risk for CB at baseline and all-cause, non-cancer and respiratory mortality (table 1); these associations were stronger in never smokers with BO, further including the association with cardiovascular mortality. Moreover, the OR for CB was 1.31 (95% CI 1.06 to 1.62) in never smokers with natural menopause and was even stronger ($p < 0.05$ for difference in OR between natural menopause and BO) in those with BO (OR 1.86, 95% CI 1.45 to 2.38). Among never smokers with hysterectomy only, early-M was only statistically significantly associated with CB. These results were similar

Table 3 MHT type and outcomes in women with natural menopause

Outcome	Never smoker		Ever smokers	
	Event, rate	Effect	Event, rate	Effect
Lung disease—emphysema *				
Oestrogen pills	16, 59	Not analysed†	59, 276	Ref
Never MHT	55, 50		394, 481	1.39 (1.04 to 1.86)‡
Oestrogen/progestin pills	17, 49		70, 229	1.11 (0.77 to 1.60)
Cancer incidence—LC§				
Oestrogen pills	8, 24	Not analysed†	52, 197	Ref
Never MHT	54, 41		386, 415	1.82 (1.35 to 2.45)¶
Oestrogen/progestin pills	11, 26		33, 90	0.62 (0.40 to 0.97)‡
Mortality§				
All-cause				
Oestrogen pills	541, 1024	Ref	562, 1369	Ref
Never MHT	3703, 1843	1.57 (1.43 to 1.72)¶	3525, 2518	1.64 (1.50 to 1.80)¶
Progestin pills	54, 618	0.79 (0.59 to 1.05)	53, 810	0.71 (0.53 to 0.95)‡
Oestrogen/progestin pills	480, 707	1.04 (0.92 to 1.18)	499, 833	0.83 (0.73 to 0.94)‡
Non-ovarian cancer				
Oestrogen pills	118, 223	Ref	159, 387	Ref
Never MHT	817, 407	1.65 (1.36 to 2.01)¶	1047, 748	1.74 (1.47 to 2.06)¶
Oestrogen/progestin pills	142, 209	1.15 (0.89 to 1.47)	164, 274	0.85 (0.68 to 1.06)
LC				
Oestrogen pills	8, 15	Not analysed†	54, 132	Ref
Never MHT	63, 31		459, 328	2.13 (1.61 to 2.84)¶
Oestrogen/progestin pills	7, 10		56, 93	0.89 (0.61 to 1.30)
Non-cancer				
Oestrogen pills	411, 778	Ref	395, 962	Ref
Never MHT	2817, 1402	1.55 (1.39 to 1.72)¶	2424, 1731	1.59 (1.43 to 1.77)¶
Progestin pills	43, 492	0.88 (0.64 to 1.20)	35, 535	0.68 (0.47 to 0.98)‡
Oestrogen/progestin pills	319, 470	0.99 (0.86 to 1.15)	319, 533	0.80 (0.69 to 0.93)‡
Respiratory				
Oestrogen pills	27, 51	Ref	77, 188	Ref
Never MHT	216, 107	1.87 (1.25 to 2.79)‡	478, 341	1.60 (1.25 to 2.05)¶
Oestrogen/progestin pills	28, 41	1.32 (0.77 to 2.25)	53, 88	0.68 (0.48 to 0.97)‡
Cardiovascular				
Oestrogen pills	180, 341	Ref	164, 399	Ref
Never MHT	1234, 614	1.47 (1.25 to 1.72)¶	1071, 765	1.62 (1.37 to 1.92)¶
Oestrogen/progestin pills	141, 208	1.03 (0.83 to 1.29)	136, 227	0.82 (0.65 to 1.03)

*Logistic regressions were performed to assess the associations (OR and 95% CI) of MHT type (never MHT, progestin pills, oestrogen/progestin pills and any MHT creams, shots or patches with oestrogen pills as the reference) with self-reported lung diseases (emphysema and chronic bronchitis). Covariates adjusted include intervention arm, age at enrolment, race (NHB and other race with NHW as the reference), education status (less than college vs some college or above), height, BMI group (underweight (BMI of ≤ 18.5 kg/m²), overweight (BMI of 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) with normal weight (BMI of 18.5–25 kg/m²) as the reference), baseline pack-years (for ever smokers) and early menopause. Rate is cases per 10 000 persons.

†Not analysed due to limited power.

‡P<0.05, compared with oestrogen pills.

§Cox proportional-hazards models were used to estimate the effect (HR and 95% CI) of MHT type (never MHT, progestin pills, oestrogen/progestin pills and any MHT creams, shots or patches with oestrogen pills as the reference) on lung cancer (LC) incidence and all-cause and cause-specific (LC, non-cancer, cancer (non-reproductive), respiratory and cardiovascular) mortality. Covariates adjusted include intervention arm, age at enrolment, race (NHB and other race with NHW as the reference), BMI group (underweight (BMI of ≤ 18.5 kg/m²), overweight (BMI of 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) with normal weight (BMI of 18.5–25 kg/m²) as the reference), baseline pack-years (for ever smokers) and early menopause. Rate is cases per 100 000 person-years.

¶P<0.001, compared with oestrogen pills.

BMI, body mass index; LC, lung cancer; MHT, menopausal hormone therapy; NHB, non-Hispanic Black; NHW, non-Hispanic White.

before (online supplemental table 4) and after (table 1) adjustment for covariates.

Associations of MHT use with health outcomes

Among ever smokers with natural menopause, ever MHT was associated with decreased risk for all health outcomes except emphysema and CB at baseline (table 2). Among those with BO, statistically significant associations with MHT were identified for increased risk for CB and reduced risk for all-cause, LC, non-cancer, respiratory and cardiovascular mortality. Moreover, the HR for cardiovascular mortality was 0.80 (95% CI 0.73 to 0.88) in those with natural menopause and 0.52 (95% CI 0.38 to 0.70) in those with BO (p<0.05 for difference in HR between natural

menopause and BO). Among those with hysterectomy only, statistically significant reductions in risk with MHT were noted for all-cause, cancer (non-ovary), non-cancer, respiratory and cardiovascular mortality. The impact of ever MHT on health outcomes did not vary by early-M status (p values for interactions >0.10, not shown). These results were similar before (online supplemental table 5) and after (table 2) adjustment for covariates.

Among never smokers with natural menopause, ever MHT was associated with reduced risk for all-cause, non-ovarian cancer, non-cancer and cardiovascular mortality (table 2). Stronger inverse associations were observed in never smokers with BO (except for non-ovarian cancer and respiratory mortality). Among never smokers with hysterectomy only, ever MHT was

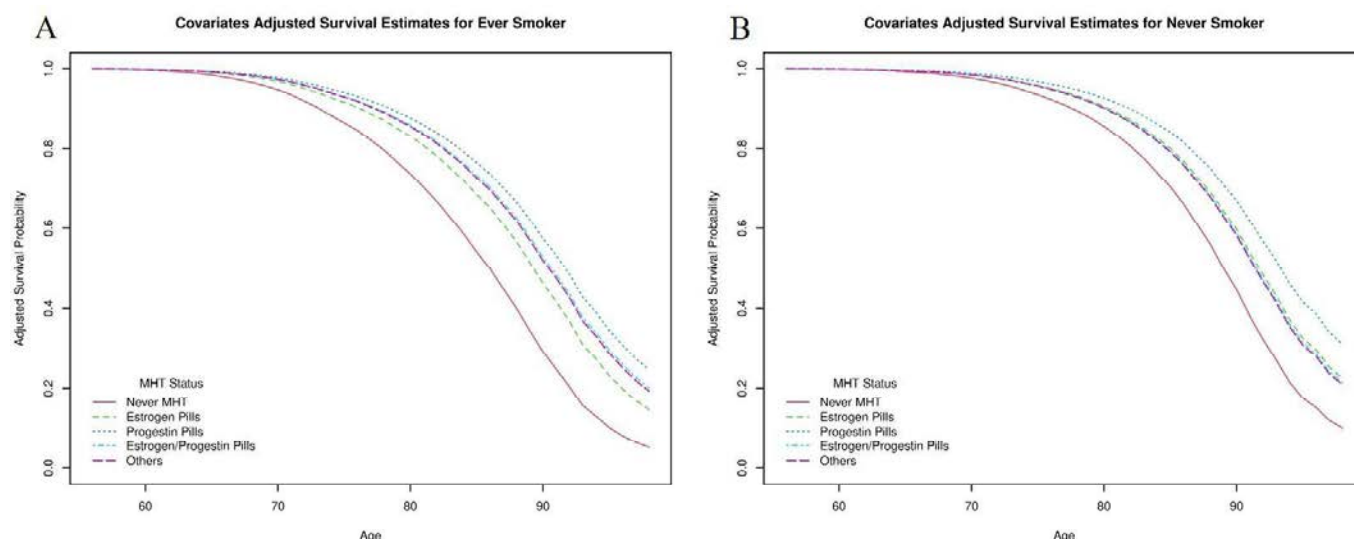


Figure 2 The effect of menopause hormone therapy (MHT) type on survival probability in ever (A) and never smokers (B) with natural menopause. MHT types include never MHT, oestrogen pills, progestin pills, oestrogen/progestin pills and others (MHT creams, shots or patches). Covariates include intervention arm, age at enrolment, race (non-Hispanic Black (NHB) and other race with non-Hispanic White (NHW) as the reference), education status (less than college vs some college or above), body mass index (BMI) group (underweight (BMI of ≤ 18.5 kg/m²), overweight (BMI of 25–30 kg/m²) and obesity (BMI ≥ 30 kg/m²) with normal weight (BMI of 18.5–25 kg/m²) as the reference), baseline pack-years (for ever smokers) and early menopause. Covariates adjusted survival probabilities were estimated using the direct standardisation method implemented in R Package ‘adjustedCurves’ (<https://cran.r-project.org/web/packages/adjustedCurves/vignettes/introduction.html>).

only significantly associated with reduced risk of all-cause and non-ovarian cancer mortality. The impact of ever MHT on health outcomes does not vary by early-M status (*p* values for interactions >0.14 , not shown). These results were similar before (online supplemental table 5) and after (table 2) adjustment for covariates. Because MHT as a binary variable was consistently associated with a reduction in all-cause mortality and certain cause-specific mortality across menopause types, we conducted further analyses to explore the associations with MHT duration reported at baseline (online supplemental table 6). When treating MHT duration as an ordinal variable, compared with never MHT use, each category of MHT duration (except for ≤ 1 year of MHT use for cardiovascular mortality in never smokers) was associated with reduced all-cause, non-cancer and cardiovascular mortality regardless of smoking status. Each category of MHT duration was also associated with reduced non-ovarian cancer and respiratory mortality in ever smokers. The greatest reduction in the HR (0.71, 95% CI 0.61 to 0.83) was seen for respiratory mortality in ever smokers who used MHT for over 10 years. We conducted an ordinal ‘dose–response’ analysis for MHT duration using the mid-value for each duration interval: 0.5 for ‘ ≤ 1 year of use’, 2.5 for ‘2–3 years of use’, 4.5 for ‘4–5 years of use’, 7.5 for ‘6–9 years of use’ and 10 for ‘ ≥ 10 years of use’, among those reporting ever MHT use. In ever smokers, greater reductions in risk were noted with longer MHT duration for all-cause ($p=0.0034$) and non-cancer ($p=0.0021$) mortality. Among never smokers who ever used MHT, no statistically significant ‘dose–response’ was found regarding MHT duration (all *p* values >0.18).

Associations of MHT type with health outcomes

Among those ($n=45\,580$) who reported ever MHT use at baseline, 24 118 subjects have information regarding type of MHT including oestrogen pills ($n=14\,856$), progestin pills ($n=895$), oestrogen/progestin pills ($n=6939$), oestrogen creams, shots or patches ($n=963$), progestin creams, shots or patches ($n=112$) and oestrogen/progestin creams, shots or patches ($n=353$). Among those with natural menopause, 35.5% and 47.6% used oestrogen pills and oestrogen/progestin pills, respectively (not shown). Women receiving BO or hysterectomy only predominantly used oestrogen pills ($>85\%$) with very few ($<3.2\%$) used oestrogen/progestin pills (not shown). Additional analyses were conducted in 33 153 women with natural menopause and type of MHT (including never MHT) to assess

whether oestrogen/progestin pills offered any different protection compared with oestrogen pills (table 3). As expected, never use of MHT was associated with adverse health effects compared with use of oestrogen pills only regardless of smoking status. Among ever smokers, taking oestrogen/progestin pills reduced LC incidence (HR 0.62, 95% CI 0.40 to 0.97) and all-cause (HR 0.83, 95% CI 0.73 to 0.94, figure 2), non-cancer (HR 0.80, 95% CI 0.69 to 0.93) and respiratory mortality (HR 0.68, 95% CI 0.48 to 0.97) compared with taking oestrogen pills only. Moreover, in ever smokers, taking progestin-only pills (compared with taking oestrogen pills) was associated with lower HR for all-cause (HR 0.71, 95% CI 0.53 to 0.95, figure 2) and non-cancer (HR 0.68, 95% CI 0.47 to 0.98) mortality.

DISCUSSION

We identified strong evidence implicating early-M as a risk factor for malignant and non-malignant lung morbidities (LC, emphysema and CB) and mortalities (LC and respiratory) as well as all-cause, non-cancer and cardiovascular mortality in ever smokers across all three menopause types. Early-M was also associated with an increased risk of CB and all-cause, non-cancer and respiratory mortality in never smokers with natural menopause or BO. Compared with never smokers, ever smokers appeared to benefit more from longer duration (>10 years) of MHT without evidence of increasing ovarian cancer mortality (see below). Oestrogen/progestin pills were generally associated with decreased risks of outcomes compared with oestrogen pills in ever smokers (but not in never smokers) with natural menopause.

We successfully replicated the results seen in the PLUSS cohort that early-M was associated with increased risk for emphysema and all-cause, non-ovarian cancer, LC and respiratory mortality in ever smokers.²⁴ With the much larger sample size in the PLCO, we also identified statistically significant associations between early-M and LC risk and cardiovascular mortality in ever smokers. Moreover, we found that respiratory illnesses, though a less common cause of death compared with cancer and cardiovascular diseases, were a cause of death most associated with early-M regardless of smoking status. Thus, we have more complete evidence to support that early-M could be a risk factor for cigarette smoking-induced malignant and non-malignant lung morbidities and mortalities. Early-M was also associated with increased risk for CB in never smokers. These findings all support the importance of maintaining lung health in women with early-M.

Our initial goal was to determine whether early-M as associated with adverse effects on lung-focused health outcomes, and if so, early-M women may benefit from targeted intervention (smoking cessation and early LC screening). We conducted additional analyses by separating late menopause (late-M, age at menopause ≥ 55) as an additional group and then comparing early-M and late-M to normal menopause (normal-M, age at menopause 45–55). This was conducted in women with natural menopause only due to low percentage of women with late-M in BO (4.1%) and hysterectomy only (0.9%). None of the outcomes tested in table 1 were significantly associated with late-M compared with normal-M in never smokers (online supplemental table 7). Among ever smokers, late-M was associated with reduced risk for all outcomes in table 1 when compared with normal-M, with emphysema, CB and all-cause, LC, non-cancer and respiratory mortality approaching statistical significance (all p values < 0.05 , (online supplemental table 7)). The strongest reductions associated with late-M were observed for emphysema (OR 0.64, 95% CI 0.48 to 0.85) and respiratory mortality (HR 0.66, 95% CI 0.52 to 0.85). Using normal-M as reference does not change the risk associated with early-M in never and ever smokers. Thus, findings in PLCO do not support late-M as a risk factor for lung diseases. We also reanalysed the PLuSS data by defining an additional variable ‘late-M’. Compared with normal-M, late-M is significantly associated with reduced risk for radiographic emphysema (OR 0.64, 95% CI 0.49 to 0.83, $p=0.0021$) and better FEV₁ at baseline (84.8 ± 29.5 mL/s, $p=0.0041$) and reduced respiratory mortality (HR 0.63, 95% CI 0.41 to 0.96, $p=0.032$) during follow-up, thus further confirming late-M may reduce subsequent lung diseases. Our results regarding late-M cannot be easily compared with other studies due to (1) selection of reference group (ours using normal-M, while others using age at menopause < 50 or < 55), (2) study design (cohort vs case-control) and (3) stratification by cigarette smoking.^{26 27}

Sudden loss of ovarian hormone production in women receiving BO provided an opportunity to explore the ‘shorter lifetime oestrogen exposure’ hypothesis which assumed that adverse effects associated with early-M were due to shorter lifetime oestrogen exposure.²⁴ Early-M in those receiving BO was associated with higher risk for lung diseases and increased all-cause and non-cancer mortality with respiratory illness as the most affected cause of death regardless of smoking status. Most importantly, early-M associations were stronger for several outcomes (eg, CB and cardiovascular mortality in never smokers and emphysema and bronchitis in ever smokers) in BO versus natural menopause with differences in magnitude of associations approaching statistical significance. Indications that trigger a BO include ovarian cysts, endometriosis and uterine fibroids, which are commonly caused by an imbalance of progesterone and oestrogen secreted from ovaries. BO may reduce the risk for breast tumours in BRCA2 mutation carriers younger than 50 years of age.²⁸ Thus, our findings identified evidence implicating early-M as a risk factor for lung diseases and non-cancer mortality (eg, respiratory and cardiovascular mortality) in never and ever smokers receiving BO. Although a trend of increasing LC incidence and mortality was identified for early-M versus non-early-M in ever smokers with BO, the associations were not statistically significant possibly due to low sample size/power in this group.

We found that early-M is a risk factor for CB and respiratory mortality in never smokers with natural menopause or BO. Late-M and MHT use were not associated with these two outcomes, suggesting the lower likelihood of involvement of female hormones in determining the susceptibility of those phenotypes in never smokers. We speculate that there may be shared mechanisms underlying lung and ovary maturation in early life that may subsequently lead to suboptimal development of both organs and functions. People with poorly developed lungs have higher risk for chronic obstructive pulmonary disease in later life without cigarette smoking, while poorly developed ovaries lead to pre-mature or early-M.^{24 29}

In this study, women with hysterectomy with ovary conservation reported a higher percentage (76.3%) of MHT use and in ever MHT users reported longer duration of MHT use compared with those with natural menopause. Two large prospective studies comparing FSH levels in women with hysterectomies and age-matched controls with intact uteri identified compelling evidence supporting a long-standing hypothesis that women with hysterectomy experience ovarian failure at a younger age.²³ Thus, it is reasonable to assume that hysterectomy received during the 1970s caused or accelerated premature ovarian ageing in a large percentage of women enrolled in the PLCO trial. In this study, associations of early-M with LC incidence and mortality, and all-cause and non-cancer mortality (eg, respiratory and cardiovascular mortality) were only statistically significant in ever smokers with magnitudes of associations similar to those seen in individuals with natural menopause. This suggests that vulnerability due to accelerated ovarian failure associated with hysterectomy is only detectable under the assault of cigarette smoking.

The importance of exogenous hormones in all-cause and non-cancer mortality (with cardiovascular mortality in particular) was also supported by consistent reduction of HRs associated with MHT use across all three menopause types regardless of smoking status. Moreover, for health outcomes with early-M as a risk factor, MHT use is likely protective. A significant MHT duration-dependent reduction in all-cause, non-cancer and cardiovascular mortality was identified in ever smokers and the HRs continued to reduce even after 10 years of MHT use. Such a trend was not identified in never smokers. Moreover, among those whose menopause was not due to BO, MHT use was not associated with ovarian cancer mortality (HR 1.00, $p=0.98$, not shown) in ever smokers, but associated with increased ovarian cancer mortality (HR 1.35, 95% CI 1.03 to 1.77, $p=0.028$, not shown) in never smokers. Thus, these results support obvious health benefit for MHT use and ever smokers benefit more from longer duration (≥ 10 years) of MHT use. We also identified evidence that oestrogen/progestin pills provided more protection compared with oestrogen pills alone in women with natural menopause.

Our studies and others²³ support age of surgery as a proxy for accelerated ovarian ageing in women receiving hysterectomy with ovarian conservation. Future studies should assess preoperative and postoperative biomarker (eg, FSH) levels in longitudinally collected blood samples to biochemically confirm the menopause and reproduce the associations identified. Current clinical guidelines universally recommend that women who undergo early-M (before age 45) be advised to use MHT, at least until the average age of menopause.^{7 30} A more comprehensive intervention strategy is needed that targets this vulnerable group and integrates medical intervention (eg, MHT and cancer screening) and lifestyle changes (eg, smoking cessation, dietary intervention and intensifying physical activity) to improve their quality of life.

A major strength of this study is that PLCO is the largest available prospective cancer-screening cohort with detailed annotation of menopause type and timing, and smoking history, which allowed us to assess the heterogeneity of associations across menopause types and cigarette smoking status, that is lacking in the literature^{31 32} but essential for developing proper analytical strategies.

This study has several limitations. First, emphysema, and LC incidence and mortality were rare in never smokers, thus power was insufficient for association analyses stratified by menopause type. Second, physician-diagnosed emphysema and CB were self-reported and no spirometry was conducted in the PLCO. However, LC incidence was confirmed by pathology report and LC and respiratory mortality was verified through a Death Review Process, thus minimising misclassification bias. Third, caution needs to be taken when generalising the results to general population as half the PLCO cohort received cancer screening targeting prostate, lung, colon and ovarian cancers, although none of the interventions reduced cancer mortality except for distal colon cancer screened by sigmoidoscopy.³³ Fourth, ever MHT use and its

duration were self-reported at baseline and were associated with health outcomes collected at baseline and during follow-up periods. Thus, the rigour of evidence may be affected by the inherent issues in observational studies. Fifth, although the PLCO offers a significant amount of geospatial and racial and ethnic diversity in assessing the associations between menopause-related variables and health outcomes, sample size in individual ethnic group other than non-Hispanic whites remains limited, thus precluding further stratification analyses.

In conclusion, this study strengthened the evidence to support smoking cessation and LC screening in smokers with natural menopause identified in the PLuSS cohort²⁴ and provided new evidence that postmenopausal women who ever smoked and had surgical menopause prior to age 45 years also should be targeted for smoking cessation and LC screening. Smokers with early-M should be targeted for smoking cessation and LC screening regardless of menopause types. Furthermore, our results also support health benefit for MHT use among ever smokers as they may benefit more from longer MHT use (10 or more years) for primary prevention of chronic diseases including lung disease. However, caution needs to be taken for clinical translation of these findings regarding MHT use as the differences in findings between the Women's Health Initiative randomised controlled trial³⁴ and this study may indicate that timing of initiating MHT use plays an important role in determining subsequent health benefits and risk.

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Contributors SL conceptualised this project, requested the PLCO data from The Cancer Data Access System (PLCO-981) and supervised the data analyses. XG, YF and HK conducted data analyses and summarised the results in tables and figures. HY, YG and SL defined early natural menopause and non-early menopause using the All of Us research program data and piloted the replication analyses, which were exclusively utilised in the peer review process. XG, YF and SL interpreted the results and drafted the manuscript. TF, KKL, YZ, JAD, SAB, LSC and SL critically edited the manuscript. SL is responsible for the overall content as a guarantor.

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Exposições ambientais associadas à pieira recorrente no início da infância na mãe e na criança na coorte de ambiente no nascimento: um estudo de tempo-até-evento

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RESUMO

Contexto

Os fatores pré-natais e as exposições ambientais contribuem para a pieira recorrente no início da infância.

Objetivo Identificar os fatores pré-natais e ambientais associados à pieira recorrente em crianças desde o nascimento até aos 48 meses na mãe e filho na coorte de ambiente, utilizando a análise do tempo-para-evento.

Método As entrevistas às mães foram realizadas durante a gravidez e no período pós-natal e as crianças foram acompanhadas desde o nascimento até aos 48 meses (maio de 2013-outubro de 2019). Os modelos híbridos de regressão e dispersão do uso do solo descreveram a exposição pré-natal residencial ao dióxido de nitrogênio (NO₂) e ao material particulado de 2,5µm de diâmetro (PM_{2.5}). O estado de pieira foi avaliado por um médico. A função de risco de Kaplan-Meier e os modelos de risco proporcional de Cox forneceram estimativas de risco, ajustadas para a exposição ao fumo do tabaco ambiental (FTA), tabagismo materno, utilização de combustível de biomassa e fatores ambientais internos.

Resultados Entre 520 pares mãe-filho, 85 (16%) crianças apresentaram um único episódio de pieira e 57 (11%) apresentaram pieira recorrente. O tempo até à pieira recorrente (42,9 meses) e à pieira única (37,8 meses) entre as crianças expostas a combustíveis de cozinha derivados da biomassa foi significativamente mais curto em comparação com as crianças com mães que utilizavam eletricidade (45,9 e 38,9 meses, respetivamente (p=0,03)). As crianças com mães expostas a FTA pré-natal apresentaram 3,8 vezes mais probabilidades de ter pieira recorrente do que as não expostas (HR ajustado 3,8, IC 95% 1,3 a 10,7). O NO₂ médio do mês de nascimento foi significativamente mais elevado na categoria com pieira recorrente em comparação com a categoria sem pieira. O NO₂ e o PM_{2.5} foram associados a um aumento ajustado de 2%-4% do risco de pieira.

Conclusão É provável que o controlo da exposição ao FTA e aos combustíveis de biomassa no período pré-natal atrase o surgimento de pieira recorrente em crianças desde o nascimento até aos 48 meses.

INTRODUCTION

Low-income and middle-income countries (LMICs) experience the highest burden of childhood respiratory disorders.¹ Studies have shown that the prenatal and the immediate postnatal period are critical windows for harmful effects from different types of exposures on respiratory health.² Wheeze in the perinatal and infant stages can be an important predictor of later childhood respiratory health.³

Childhood wheezing comprises a spectrum of presentations, ranging from transient to recurrent or multiple trigger wheeze, with a substantial proportion associated with asthma.⁴ The prevalence trends of childhood and adolescent current wheeze adolescents have varied in LMICs but have been stable in high-income countries.⁵ In Europe,

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Maternal and environmental tobacco smoke exposure, exposure to biomass or fossil fuels and ambient pollution in the antenatal period increases the risk for adverse respiratory outcomes in infants. The risk for recurrent wheeze in early infancy associated with these exposures is less well established. Recurrent wheeze is an important predictor of childhood asthma.

WHAT THIS STUDY ADDS

► Biomass fuel exposure and environmental tobacco smoke exposure increased the risk for recurrent wheeze in infants from birth to 4 years of age. There was a suggestion that ambient pollution, as measured at birth, may be a risk factor for this outcome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Low-cost interventions to reduce environmental exposures must be implemented in the antenatal period while cleaner fuel usage strategies are necessary in low socioeconomic communities. Further evidence is necessary to understand the relationship between ambient air pollution on recurrent wheeze in infancy.

studies have reported the prevalence of ever wheezing children diagnosed with asthma by the age of 4 years ranged from 15.9% in Spain to 39.5% in England.⁶ The prevalence of wheezing in infants has been reported at 15.9% (95% CI 14.0% to 18.0%) in African countries.⁷ These wheezing episodes are, in the majority, mild, episodic and responsive to therapy. Approximately 30% of children experience recurrent wheezing during the first 5 years of life, and this can be associated with significant morbidity.⁸

Persistent wheeze at school age is associated with a range of predictors. These include colds and respiratory tract infections, exercise, parental asthma or allergy, eczema, allergic rhinitis, allergic sensitisation and eosinophilia.⁹ Maternal smoking during pregnancy and exposure to tobacco smoke antenatally and postnatally has been shown to alter lung development, increase susceptibility to lower respiratory tract infections and increase the prevalence

of wheezing.¹⁰ The presentation of preschool persistent wheeze, in the absence of colds or exercise-induced asthma, may be an important indicator of some environmental trigger. In the Drakenstein Child Health Study, antenatal and early life exposure to environmental tobacco smoke (ETS) was associated with lower respiratory tract infection with associated wheeze in 43% of cases.¹¹

Early-life exposure to biomass fuel has been shown to affect children's respiratory health outcomes both in the short term and long term.¹² In a meta-analysis of eight studies, the risk of acute respiratory tract infection in children exposed to biomass fuels was three times greater than those not exposed.¹³ Children exposed to smoke biomass fuels in two Nigerian studies had an 8.7% and 5.1%, 12-month prevalence of reported wheezing, respectively.¹⁴ Few studies have investigated biomass fuel exposure and wheezing frequency in infancy.

Air pollution is associated with adverse respiratory health, particularly in early infancy when rapid lung growth occurs. Postnatal exposure to air pollution (nitrogen dioxide (NO₂), fine particulate matter 2.5 µm diameter (PM_{2.5}, PM₁₀) and sulfur dioxide (SO₂)) were associated with an increased incidence of wheezing in European children.^{15–16} Antenatal and early life exposure to tobacco smoke resulted in an increased risk of infant wheezing in the presence of exposure to increased levels of PM₁₀ and NO₂.¹⁷ Indoor air quality has been reported with increased risk of adverse respiratory outcomes among infants.¹⁸ Other maternal risk factors associated with infant respiratory health include alcohol consumption during pregnancy.¹⁹

Recurrent wheeze in infancy, an established marker of childhood asthma⁸ and associations with environmental factors have not been extensively reported in the literature. The 'time-to-event'²⁰ and the HR (the ratio of two instantaneous rates of an event at any time during follow-up)²¹ provide estimates of association in a cohort analysis. In a recent time-to-event study among 5788, Chinese children aged 3–5 years, an increased HR for antenatal and PM exposure in the first year of life was reported for asthma, but not for wheeze.²² Time to wheeze studies are limited, particularly those investigating potential risk factors in children from birth through to the first few years of life. We hypothesised that environmental factors, such as air pollution, indoor air quality, maternal smoking and ETS, are likely to be associated with recurrent wheeze in early childhood, resulting in an earlier diagnosis of this outcome. We used a time-to-event analysis to determine the impact of antenatal and environmental risk factors associated with recurrent wheezing in children (birth to 48 months) from the mother and child in the environment (MACE) birth cohort in Durban, South Africa.

METHOD

Setting

The MACE birth cohort is an ongoing study designed to investigate the risk of environmental pollutant exposure commencing in utero on the long-term respiratory health of children.²³ The study is located in communities in the south (high industry/residential mix) and north (less industrialised) of Durban, South Africa.

Sample selection

The selection of pregnant women into the MACE cohort has been described previously.²³ In brief, pregnant women attending the public sector antenatal clinics in the south and north communities of Durban, South Africa, meeting the inclusion criteria, were selected. The inclusion criteria included residence in the geographical area for the duration of the pregnancy and the period of follow-up. Those with multiple pregnancies were excluded, however, no pregnancy complications or health conditions were used as exclusion criteria. Mother and child pairs (n=520), who had attended one or more clinical follow-up visits, were included in this analysis. The children were followed up from birth to 48 months at the local hospitals. The mother–child pairs who did not attend any clinic visit were excluded (n=80), and they did not significantly differ from the included pairs (online supplemental table 1 and online supplemental figure 1).

Data sources

Pregnant females participated in interviews at recruitment and during each trimester of pregnancy. Interviews included questions on antenatal risk factors (age, general health and reproductive history; education, income, residential, housing type, alcohol and smoking history, indoor mould and dampness); antenatal ETS exposure (exposure to passive smoking at home and/or work), biomass and fossil fuel exposure, childhood respiratory problems, family history of asthma and tuberculosis. These instruments were based on previously validated questionnaires, such as the National Health and Nutrition Examination Survey.²⁴ Postnatal child data included infant sex, age, birth weight, gestational age and HIV status.

Clinical assessments

Clinical assessments were conducted at 6, 12, 24 and 48 months by a paediatric pulmonologist. Developmental and nutritional status was assessed with the aid of the WHO growth charts and standards.²⁵

The main outcome variables in this study were the presence of wheezing episodes which was assessed through multiple approaches: (1) maternal reporting at each clinical visit (in response to the specific question, 'Did your child ever have a wheeze (whistling sound from the chest) in the last 12 months?'; (2) review of the child's 'Road-to-Health' record (a comprehensive documentation of primary healthcare and health services visit of every South African child from birth) supported by the reported use of nebulisations and (3) a clinical assessment performed by specialist medical officers at the clinic visit. The medical officers conducted the detailed wheeze interviews and the assessment of the corroborating evidence as outlined above, including determining whether the wheeze episode was associated with any viral infections. Single wheeze was defined as one episode of wheeze determined at any clinical visit during the 48-month follow-up and recurrent wheeze was defined as two or more episodes of wheezing over this follow-up period. The timing of each wheezing episode was documented but recorded as per the date of the clinical assessment.

Environmental monitoring

A hybrid atmospheric dispersion/land use regression model for the prediction of air pollution concentrations in Durban, South Africa was developed for the MACE cohort.²⁶ Statistically significant hybrid models (incorporating geographical and dispersion modelling inputs) were developed for the various pollutants of interest, NO₂ and PM_{2.5}. The specific methodology, identified predictor variables and the goodness of fit of these hybrid models have been previously described.²⁶

This model was applied to estimate an annual average ambient exposure level at the address of each MACE participant. These annual average concentrations were adjusted for an estimate of maternal exposure during the first trimester of the pregnancy and the month of birth of the child using continuous monitoring values (based on successive 2 week exposures of Radiello tubes over the course of a year) at a reference site.²⁷ The adjustment was to cover the period of the pregnancy, which would fall across seasons. The weighting was based on continuous ambient measurements for one full year.

The rationale for this adjustment was to better characterise exposure during the pregnancy, which may be biased by the use of an annual average, as the monthly variation in air pollution is not captured in the latter metric. The ratio of the average pollutant concentrations at the reference site during each participant's first trimester period and month of birth, to the annual average concentration at the reference site was used to adjust the annual average exposure value calculated for the participant's address to represent the first trimester (online supplemental equation 1) and month of birth (online supplemental equation 2), respectively, as described further in online supplemental material. This adjustment procedure assumes that variation in ambient air quality at the participant's addresses are consistent with those at the reference site. This is a reasonable assumption given the proximity of the reference

Table 1 Maternal and infant demographics in MACE birth cohort (n=520)

Characteristics	Wheezing (%)			P value
	No wheeze n=378	Single wheeze n=85	Recurrent wheeze n=57	
Mother education				0.707
<Secondary school education	24.9	31.8	24.6	
Matric (high school graduate)	58.2	55.3	57.9	
College/technikon/university	16.9	12.9	17.5	
Mother's yearly gross income (US\$)				0.459
None	47.6	51.8	56.1	
<US\$650	20.4	20.0	10.5	
US\$650–US\$2000	18.0	18.8	17.5	
>US\$2000	10.8	7.1	15.8	
Refused to answer	3.2	2.4	0.0	
Housing type				0.986
Formal	83.3	83.5	84.2	
Informal	16.7	16.5	15.8	
Maternal age (mean (SD))	26.2 (5.9)	26.0 (6.4)	26.3 (6.2)	0.938
Infant sex (male)	52.1	56.5	59.6	0.483
Infant age				
6	21.7	8.2	0.0	0.000
12	23.5	30.6	24.6	
24	22.5	24.7	15.8	
36	14.0	15.3	21.1	
48	18.3	21.2	38.6	
Birth weight (mean (SD))	3149.2 (538.6)	3050.4 (599.6)	3184.8 (502.1)	0.251
MACE, mother and child in the environment.				

site to the participant addresses and that this reference site was selected to reflect general fluctuations in ambient concentrations, as opposed to capturing local emission patterns (eg, as a traffic site or industrial reference site would).

Statistical analysis

Data management, descriptive statistics and time-to-event analyses were performed using STATA V.15.0 for Windows (STATA). Descriptive statistics were used to describe participants' characteristics related to the outcome variables (single and recurrent episodes of wheezing). Variables that were investigated included maternal risk factors (age, maternal health, education, income, residential, housing type); neonatal risk factors (infant sex, age, birth weight, preterm birth, HIV exposure) and childhood environmental exposures (maternal alcohol history, antenatal ETS exposure, indoor mould and dampness, energy source for cooking and heating, family history of asthma). Two air pollution exposure metrics were applied for each outcome for each participant: a proxy measure for the first trimester and another at the month of birth. χ^2 tests for categorical variables and Student's t-tests for continuous variables were applied in the univariate analysis.

The Kaplan-Meier (KM) hazard function was used to estimate the probability of time (age in months at clinical visit) to document a single wheeze episode and time to document recurrent wheezing. The proportional hazard assumption was assessed using the log-negative log-survival plot (the 'parallel lines test'). The assumption was satisfied. Patients were censored on the last visit time if lost to follow-up or if no wheeze was recorded at the end of the 48-month follow-up. The advantage of this analytical strategy meant that those who attended a single visit over the 4-year period could still contribute data up to the point of their attendance and did not need to be excluded from the sample a priori.

The following variables were considered in the multivariable models: child gender, antenatal ETS, maternal alcohol consumption, family history of asthma, sources of energy at home and the predicted average ambient exposure level $PM_{2.5}$ and NO_2 during

the first trimester of the pregnancy and the month of birth of the child, as described above and in online supplemental material.

The proportional hazard assumption was assessed, and all the independent variables satisfied the assumption. The Cox-proportional hazard model was used to assess the relationship between the predictor variables and single and recurrent wheezing episodes. Each variable was tested to see if it was a significant predictor of the occurrence of single and recurrent wheezing using univariate χ^2 , ANOVA and Cox regression. The univariate Cox-regression analysis was used to estimate the unadjusted HRs. All variables with $p < 0.25$ in the univariate analysis were candidates in the stepwise (backward likelihood ratio) multivariate Cox regression model. The association of single and recurrent wheezing with ambient exposure to NO_2 and $PM_{2.5}$ was also analysed using Cox-proportional hazards regression models. The adjusted HR was expressed as the effect of a $1 \mu g/m^3$ increase in ambient exposure in the child's residential address. We ran all two-way interactions in the final model and none of them were found to be significant.

RESULTS

Of the 760 live births in the cohort, 520 children attended at least one clinical visit: 442 (85%) at 6 months, 396 (76%) at 12 months, 254 (49%) at 24 months, 153 (29%) at 36 months and 114 (22%) at 48 months. Relocation from the study area ($n=171$ (21.7%)) was the most common reason for loss to follow-up. There were no demographic differences between those included in this analysis and those excluded (online supplemental table 1). Participants were from low socioeconomic backgrounds (50% had completed high school and a similar percentage with no annual income) with a mean maternal age at recruitment of 26.1 (SD=5.9) years. Of the 520 clinic attendees, 378 (73%) reported no wheezing episodes, 85 (16%) reported a single wheeze and 57 (11%) reported recurrent wheeze. The mean current weight and height of the children in the three groups were similar with 86.9% having a normal BMI and 8.3% being overweight (table 1). There were no meaningful

Table 2 Risk factors associated with child wheezing (n=520)

Characteristics	Wheezing		
	No wheeze n=378 %	Single wheeze n=85 %	Recurrent wheeze n=57 %
Current maternal smoking	4.2	5.9	7.0
Antenatal ETS	48.9	57.6*	77.2**
Maternal antenatal alcohol consumption	7.6	4.9**	21.4**
Low birth weight	10.3	17.6*	5.3
Preterm birth	12.4	11.8	8.8
Infant HIV exposed	35.2	34.1	33.3
Syphilis positive	5.9	10.6*	1.8
Family history of asthma	14.3	20.0	21.1
Maternal BMI			
Underweight	4.0	1.2	7.0
Normal	34.0	42.4	29.8
Overweight	30.8	30.6	21.1
Obese	31.3	25.9	42.1
Child BMI			
Normal	79.2	86.9	86.0
Underweight	4.9	3.6	3.5
Overweight	10.4	8.3	3.5
Obese	5.5	1.2	5.3
Mould mildew			
Yes	12.3	20.0	15.8
Energy sources for cooking			
Electricity	97.9	96.5	94.7
Biomass fuels	0.8	1.2	1.8
Paraffin	1.1	1.2	1.8
Other	0.3	1.2	1.8
Air pollution exposure mean (SD)			
Birth month NO ₂ (µg/m ³)	14.9 (6.6)	16.7 (8.0)**	16.6 (7.3)*
First trimester NO ₂ (µg/m ³)	17.5 (5.8)	16.5 (5.6)	16.3 (5.4)
Birth month PM _{2.5} (µg/m ³)	11.4 (5.0)	12.6 (5.4)*	12.4 (5.3)
First trimester PM _{2.5} (µg/m ³)	13.5 (4.3)	12.7 (4.4)	12.3 (3.9)*

Calculated as per equation s1 and 2 shown in the online supplemental material.

*p<0.05; **p<0.01 when compared to the 'no wheeze' group.

BMI, body mass index; ETS, environmental tobacco smoking.

differences between the two wheeze groups when compared with the no-wheeze group.

Among the recurrent wheeze group, a higher proportion of children were exposed to antenatal ETS, maternal obesity and antenatal alcohol consumption when compared with the no wheeze and single wheeze groups. Antenatal maternal alcohol consumption was 3-fold more prevalent among the children with recurrent wheeze when compared with the non-wheezing group while antenatal ETS exposure was almost 1.6-fold higher across these categories (table 2). A family history of asthma was similar among those with a single (20%) and recurrent episodes of wheezing (21%), but higher than those without wheeze (14%). The indoor mould mildew (15%–20%) did not vary across the wheeze categories (table 2).

Both NO₂ and PM_{2.5} calculated at birth were higher among the recurrent and single wheeze categories than those without wheezing. This relationship was reversed when using exposure metrics in the first trimester. The NO₂ measure at birth between the recurrent wheeze category and no wheeze reached a statistically significant difference (16.7 µg/m³ (SD 7.3) and 14.9 µg/m³ (SD 6.6), respectively) (table 2).

The time to having single and recurrent wheezing among children with antenatal ETS exposure was shorter relative to those children without exposure to antenatal ETS, as shown in the hazard (KM) curves in (figure 1A and figure 2A). For children from a mother exposed to antenatal ETS, the mean time to single wheeze and to recurrent wheeze was 37.1 months and 45.4 months, respectively. Similarly, the KM curves showed a shorter time to single and recurrent wheeze for children whose household used biomass or fossil fuels, compared with those using electrical sources only (figure 1B and figure 2B and online supplemental table 2). These differences were statistically significant (p<0.05) (online supplemental table 2).

Children from mothers exposed to antenatal ETS had an approximately 1.7 times higher risk of single wheeze (adjusted HR 1.69 (95% CI 1.1 to 2.6)) and 3.8 times higher risk of recurrent wheeze adjusted (HR 3.76 (95% CI 1.3 to 10.6)) (table 3) than children with mothers not exposed to antenatal ETS. Exposure to biomass fuels showed a threefold adjusted increase in risk for recurrent wheeze (HR 3.09 (95% CI 0.91 to 10.45)) (table 3). Neither single nor recurrent wheezing was significantly associated with exposure to NO₂ or PM_{2.5}. Per unit increase in pollutant (both NO₂ and PM_{2.5}) measured in the month of birth, resulted in a 2%–4% adjusted increase in risk for single or recurrent wheeze compared with no wheeze, although these did not reach statistical significance. This pattern was absent for the exposure in the first trimester of pregnancy (table 3).

DISCUSSION

In this study, time to single and recurrent wheeze were significantly reduced with exposure to antenatal ETS or biomass or fossil cooking fuels as compared with no exposure. Additionally, the latter agents and ambient pollution at birth showed an increased risk for these outcomes, although not always statistically significant when adjusting for other covariates.

Few studies have investigated 'time to recurrent wheeze', considering environmental exposures at different time points (antenatally and postnatally), within a cohort followed up in infancy. These findings suggest a reduced time to recurrent wheeze, an important predictor of childhood asthma,⁸ presents with important clinical significance. Low-cost interventions to reduce antenatal ETS exposure and biomass or fossil fuel usage at an individual level are possible, and our findings suggest that these could have important health benefits.

There is evidence that ETS presents with a short-term risk, as well as increasing the risk for longer-term adverse health. Both antenatal and postnatal maternal smoking increased the risk of wheezing and persistent wheeze in early life.^{28 29} Other studies, from LMICs, have also shown this association.^{30 31} In addition to our findings providing additional support for the association of antenatal ETS exposure with wheezing, we were able to show that among those with recurrent wheeze, the onset of wheeze is significantly sooner among exposed children.

Biomass fuel exposure is a well-recognised cause of respiratory disease.³² An increase in the prevalence of wheeze among pre-schoolers has been associated with exposure to biomass fuels in indoor environments in early infancy.³³ In our study, the time to recurrent wheeze was significantly related to biomass fuels. Even though a small percentage of participants were exposed to these energy sources, a significant association with recurrent wheezing (OR 3.37 (95% CI 1.03 to 11.05)) was observed. There have been a few studies that have reported exposure to indoor air quality and the association to childhood wheezing.¹⁸ Maternal alcohol consumption has been shown to increase the risk of impaired lung function in infants,¹⁹ however, in our findings although alcohol consumption was high in mothers of recurrent wheezers there was no association between maternal alcohol intake and recurrent wheezers.

There was a statistically significant higher mean NO₂ month of birth exposure among the recurrent wheeze category compared with the non-wheeze category. This relationship was not seen

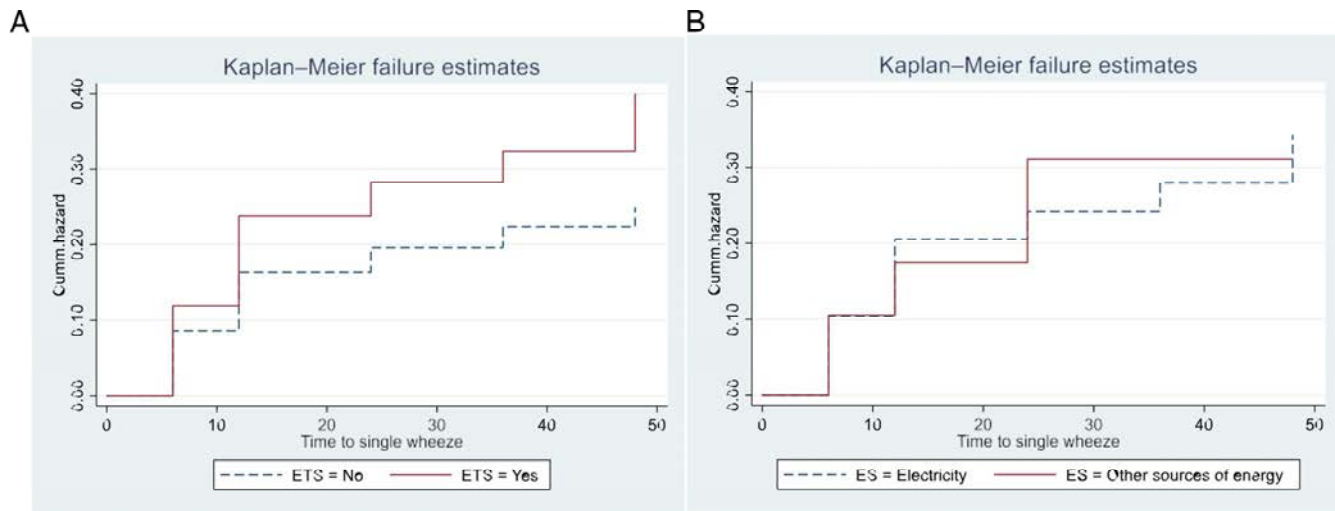


Figure 1 Kaplan-Meier curves for the hazard of single wheezing according to (A) antenatal environmental tobacco smoke (ETS), (B) energy sources (ES). (Cum hazard is the accumulated risk of experiencing single wheezing).

when exposures from the first trimester were considered. Similarly, the adjusted HRs for pollutants at the time of birth NO_2 -related single and recurrent wheeze were increased, suggesting a pollutant-related risk, but with CIs including the null. We did not show any relationship between wheeze to $\text{PM}_{2.5}$ exposure levels. In a recent time-to-event analysis, every 10 mg/m^3 rise in prenatal PM exposure, resulted in an increased HR for childhood asthma of 1.6 (95% CI 1.16 to 2.3), 1.3 (95% CI 1.1 to 1.6) and 1.2 (95% CI 0.05 to 1.5) with PM_{10} , $\text{PM}_{2.5}$ and PM_{10} , respectively.²⁰ Significant associations between higher prenatal and early life $\text{PM}_{2.5}$ exposure and ever wheeze (RR 3.76 (95% CI 1.4 to 10.0) per 5 $\mu\text{g}/\text{m}^3$ increase in pollutant) and current wheeze in the past year (RR 7.91 (95% CI 1.5 to 41.6) per 5 $\mu\text{g}/\text{m}^3$ increase in pollutant) were reported among children born to mothers in a sample of 536 children in Mexico City.³⁴ This is similar to the reported relationship of pollutant levels with recurrent wheezing in other studies, where estimates of risk ranged from OR 1.18 (95% CI 1.1 to 1.3) to OR 3.58 (95% CI 1.2 to 10.8).^{35 36} To explore whether our models were influenced by our use of a change in 1 $\mu\text{g}/\text{m}^3$ unit increase in pollutant as compared with a change in IQR, we performed a sensitivity analysis using the IQR. The estimates from this analysis are shown in online supplemental table 3a,b. The adjusted HR estimates for the exposure variables varied only slightly but did not change in statistical significance.

The lack of a statistically significant association with ambient pollutants in our study may be a result of our exposure characterisation. Although we created regression models to describe ambient

pollutant concentration at the household level during the antenatal period, no systematic assessment was performed to determine exposure in the postnatal period during which the outcomes were assessed. To attempt to address this, we developed proxy measures of exposure based on a month of birth and the trimester of conception. These two proxy measures reflect exposure during the period that is most likely to impact the morphology of the growing lung. However, simultaneously, our outcome of interest (wheeze) is likely to be affected by a shorter and more recent exposure measure. This was not captured in this analysis and may account for the absence of a statistically significant pollutant-related effect. This apriori choice of exposure metrics was based primarily on our objective to determine the effect of antenatal exposures on the outcomes. We were post hoc constrained in developing postnatal exposure metrics for specific time points (such as for each clinic visit or each wheeze episode) because of the computational demands in creating new exposure metrics. Of interest though was the differences seen in the first trimester and birth month measures, with the latter suggesting more important relationships. Despite the possibility of these being chance findings, it may imply that more recent postnatal ambient pollutant exposures influence wheeze outcomes as compared with antenatal exposures.

Recurrent wheezing is a common symptom of illness during infancy and early childhood.^{37–40} The prevalence of recurrent wheezing in infancy has been reported at between 14.3% and 36.6%, declining to 17.3% and 12% in the second and third year, respectively, among infants in Arizona.³⁷ Other reported risk factors for

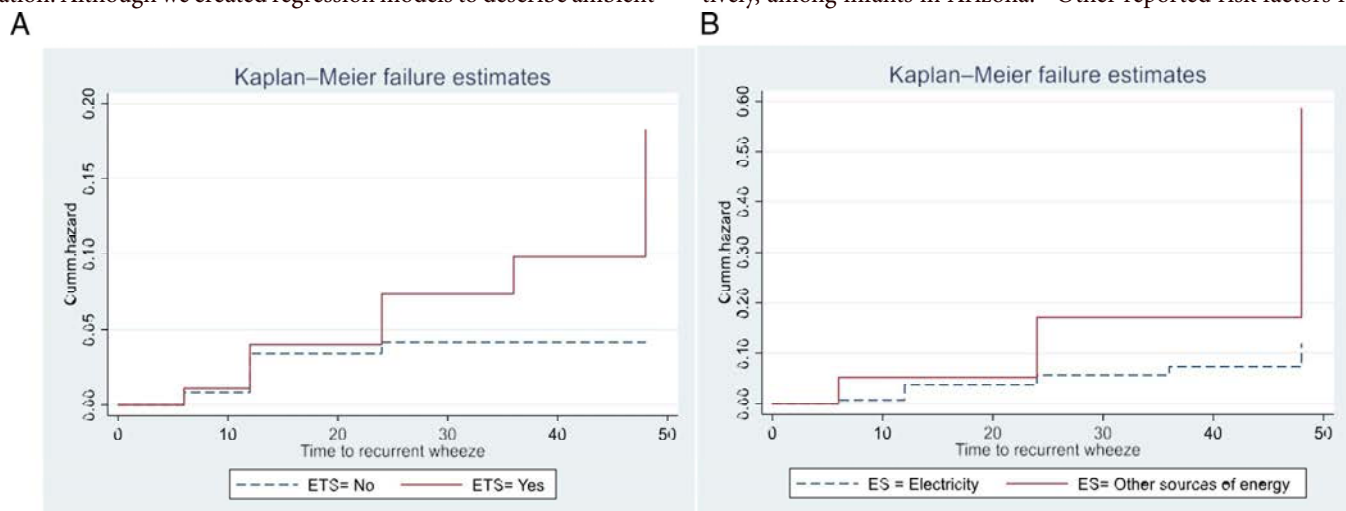


Figure 2 Kaplan-Meier curves for the hazard of recurrent wheezing according to (A) antenatal environmental tobacco smoke (ETS), (B) energy sources (ES). (Cum hazard is the accumulated risk of experiencing recurrent wheezing).

Table 3 Unadjusted and adjusted Cox-proportional hazards model for risk factors that contribute to single and recurrent episodes of childhood wheezing (n=520)

Variables	Child wheezing							
	Single wheezing (n=85)				Recurrent wheezing (n=57)			
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Child gender								
Male	1.27 (0.89 to 1.82)	0.192	1.14 (0.79 to 1.65)	0.483	1.27 (0.63 to 2.54)	0.493		
Female	1				1			
Antenatal ETS								
Yes	1.53 (1.06 to 2.22)	0.024	1.69 (1.11 to 2.56)	0.014	2.28 (1.03 to 5.06)	0.043	3.76 (1.33 to 10.66)	0.013
No	1				1			
Maternal alcohol consumption								
Yes	1.45 (0.83 to 2.53)	0.195	1.27 (0.74 to 2.20)	0.408	1.77 (0.68 to 4.58)	0.241	1.07 (0.34 to 3.36)	0.914
No	1				1			
Family history of asthma								
Yes	1.30 (0.84 to 2.01)	0.234	1.36 (0.87 to 2.14)	0.179	0.55 (0.20 to 1.57)	0.264	0.59 (0.20 to 1.72)	0.332
No	1				1			
Energy sources for cooking								
Biomass or fossil fuels	0.96 (0.35 to 2.59)	0.932	1.00 (0.36 to 2.76)	0.998	3.37 (1.03 to 11.05)	0.045	3.09 (0.91 to 10.45)	0.069
Electricity	1				1			
Birth month NO ₂ *	1.01 (1.00 to 1.05)	0.291	1.02 (0.99 to 1.04)	0.206	1.04 (1.00 to 1.08)	0.080	1.03 (1.00 to 1.08)	0.146
First Trimester NO ₂ *	0.98 (0.95 to 1.01)	0.127	0.97 (0.94 to 1.00)	0.078	0.97 (0.93 to 1.03)	0.346	0.95 (0.91 to 1.01)	0.071
Birth Month PM _{2.5} *	1.01 (0.98 to 1.05)	0.390	1.02 (0.98 to 1.05)	0.292	1.04 (0.98 to 1.11)	0.210	1.04 (0.97 to 1.10)	0.282
First Trimester PM _{2.5} *	0.97 (0.93 to 1.01)	0.166	0.96 (0.92 to 1.01)	0.077	0.94 (0.86 to 1.01)	0.106	0.95 (0.87 to 1.03)	0.186

HR is significant at $\alpha=0.05$.

Bold values are statistically significant.

*Per one unit increase of pollutant ($\mu\text{g}/\text{m}^3$).ETS, environmental tobacco smoke; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter of 2.5 μm diameter.

recurrent wheeze include male sex, mycoplasma infection and home smoke exposure,³⁸ severe pneumonia, low birth weight³⁹ and gastro-oesophageal reflux.⁴⁰ In our sample, approximately 27% reported wheeze, and 11% of recurrent wheeze occurred in children with lower respiratory tract infection (LRTI), and ETS emerging as a key risk factor in keeping with the previously reported findings. Some of these factors, in keeping with our findings, also suggested a shorter time to recurrent wheeze.³⁸

Recurrent wheeze has been shown to be an important determinant of the development of childhood asthma in the European population. It has been reported that 21.6% who present with recurrent wheeze in early childhood progressed to childhood asthma by the age of 7 years,⁴¹ with asthma prevalence associated with an increase in the number of family members affected with asthma.⁴² In our findings, although an increasing trend in prevalence existed for family history of asthma in the different wheeze categories (14% among those without wheezing; 20% among single wheezing and 21% among recurrent wheezing), we were not able to objectively test for asthma.

Our paper has numerous strengths. This mother–child longitudinal birth cohort has rigorously collected outcome and covariate data over the antenatal period and up to 5 years of age. This is the first study in Africa that used a novel data-driven statistical method using KM curves to identify time-to-event (single or recurrent wheezing) episodes. The association between time to single and recurrent wheezing was associated with ETS and biomass fuels and suggestive of a relationship with ambient pollution, and this warrants a continuation of study follow-up to further investigate the possibility of childhood asthma.

Our analytical approach, using a time-to-event strategy meant that we were able to use all data provided by participants in the cohort, and not restricted just to those with multiple visits. To assess the validity of our results, the proportional hazard assumption

was assessed using the log-negative-log-survival plot (parallel lines test). This assumption was satisfied.^{43–44} The cohort design allowed for the collection of key time-related covariates which could be adjusted for in the analysis.

Apart from the exposure characterisation limitation described above, the assessment of outcome (single and recurrent wheeze) may have presented as a limitation. Generally, these are reliant on parent/caregiver reporting wheezing episodes, and this may have been subjected to recall bias. Our use of standardised questions from well-documented epidemiological studies, such as The National Health and Nutrition Examination Survey (NHANES) allows us to compare across studies. We believe that our assessment approach is a strength of our study. Outcomes were assessed by paediatric pulmonologists and experienced clinicians and were not simply dependent on questionnaire responses. Additionally, the child health record, the monthly questionnaire and other medical records together with the physician-diagnosed wheezing that occurred at follow-up visits were used in the classification of the wheezing categories.

We were not able to include the entire cohort in our analysis, as some participants (n=80) did not attend any clinic visits during the 48-month review period. However, we do not believe that this non-participation biased our findings, as there were no meaningful differences between these two groups (online supplemental table 1).

In conclusion, prenatal exposure to passive smoking and use of biomass energy sources were risk factors associated with time to recurrent wheezing in this birth cohort over the first 48 months of life. At the time of birth, NO₂ was related to single and recurrent wheeze were increased, suggesting a pollutant-related risk. These findings, therefore, support emerging evidence that antenatal ETS and exposure to air pollution might influence the development of recurrent wheezing in children.

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Contributors RNN is the overall PI of the study, conceptualised the study design, together with PMJ, who were jointly responsible for the clinical assessments. PMJ, as the paediatric pulmonologist, was responsible for the clinical instruments. KA was responsible for drafting the manuscript, contributed to the study design and was responsible for fieldwork, data acquisition and management. AAAM was the lead for the data analysis, and this was further developed and interpreted by RNN, PMJ and KA. LR was responsible for the exposure assessment. All coauthors commented on and contributed to the advanced drafts of the manuscript, including the final submitted version, and versions subsequently revised through the peer-review process. The author(s) read and approved the final manuscript. The guarantor in the statement below is RNN.

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Os perfis metabólicos e imunitários urbanos das vias respiratórias aumentam o risco de infecções no início da infância

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RESUMO

Contexto As infecções na infância continuam a ser uma das principais causas mundiais de mortalidade infantil e as exposições ambientais parecem ser de suma importância. Investigamos se a urbanidade à nascença estava associada ao risco de infecções e exploramos os mecanismos subjacentes.

Métodos As crianças (n=633) da coorte mãe-filho COPSAC2010 foram monitorizadas diariamente com diários de sintomas de episódios de infecção durante os primeiros 3 anos e diagnosticadas prospectivamente com asma até aos 6 anos de idade. Os ambientes rurais e urbanos foram baseados na base de dados CORINE Land Cover. O perfil imunitário das vias respiratórias das crianças foi medido às 4 semanas de idade. O perfil metabólico materno e da criança foi avaliado à 24ª semana de gravidez e à nascença, respetivamente.

Resultados Observámos uma média (DP) do número total de infecções de 16,3 (8,4), consistindo principalmente em infecções respiratórias superiores até aos 3 anos de idade. A vida urbana versus rural aumentou o risco de infecção [17,1 (8,7) vs. 15,2 (7,9), rácio da taxa de incidência ajustada; 1,15 (1,05–1,26), p=0,002] e alterou o perfil imunitário das vias respiratórias da criança, o que aumentou o risco de infecção [componente principal 1 (PC1): 1.03 (1.00–1.06), p=0.038 e PC2: 1.04 (1.01–1.07), p=0.022]. A vida urbana também alterou os perfis metabólicos maternos e da criança, o que, por sua vez, aumentou o risco de infecção. A associação entre urbanidade e risco de infecção foi parcialmente mediada pelos perfis metabólico materno e imunitário das vias respiratórias da criança. Finalmente, a urbanidade aumentou o risco de asma aos 6 anos de idade, o que foi mediado pela carga de infecção precoce (pACME <0,001).

Conclusão Este estudo sugere que a urbanidade é um fator de risco independente para infecções precoces, parcialmente explicado por alterações no início do desenvolvimento metabólico e imunológico, com implicações para o risco posterior de asma.

INTRODUCTION

Infections in early childhood remain a leading global cause of child morbidity and mortality.¹ The large infection burden is associated with significant health-related costs.² Further, respiratory tract infections in particular have been associated with later development of diseases such as asthma and allergy.^{3,4} A recent Danish nationwide study also found a higher risk of developing any mental disorder by having a large infection burden in early childhood suggesting common infections to have multiple organ consequences.⁵

During the first years of life, children experience several different common infections with a large variation in individual susceptibility. It remains a challenge to identify which children are more prone than others and to understand the mechanisms driving infection proneness in otherwise healthy young children. Prenatal and postnatal environmental

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Previous studies have investigated potential risk factors for infection proneness in young children. However, no large cohort study including several mechanistic data layers has explored the potential influence of living environment in pregnancy and early childhood.

WHAT THIS STUDY ADDS

► We are the first large longitudinal cohort study to investigate the association between perinatal urbanicity, early infection burden and later asthma risk and identify underlying explaining mechanisms using several mechanistic data layers. We showed this association to be explained by alterations in the maternal and child metabolomic profile and child airway immune profile reflecting living environment. This study is strengthened by the unique close longitudinal follow-up and daily registration of infection episodes from birth until age 3 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Our study suggests urbanicity as an independent risk factor for infection development and identifies potential mechanistic reasons for this association that could be used in a disease prevention approach in future studies.

exposures have been suggested to play a key role in infection proneness⁶ and we recently demonstrated a link between an early urban living environment and risk of later asthma and allergy.⁷ However, it is unknown whether urbanicity could also influence the risk of infections and which mechanisms might explain such a relationship.

We hypothesised that urban living in early life was associated with higher risk of infections compared with living in a rural environment. To study this, we used clinical data from our prospective Danish population-based Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) 2010 cohort, where we followed the mothers during pregnancy and their newborn children with daily diaries on infections during the first 3 years of life. We integrated a comprehensive amount of data on environ-

mental exposures, genetics, the early life metabolome, microbiome and airway immune profiles to explain potential underlying driving mechanisms. Finally, we investigated the relationship between urbanicity, infection burden and later asthma risk until age 6 years.

METHODS

The study population and baseline characteristics of the COP-SAC₂₀₁₀ cohort have previously been described in details.^{8,9} In brief, 700 mother–child pairs were followed from pregnancy week 24 and through childhood until age 3 years with longitudinal deep clinical phenotyping in the COPSAC clinic where they underwent nine planned visits from week 1 until age 3 years at age 1 week, 1 month, 3 months, 6 months, 1 year, 18 months, 2 years, 30 months and 3 years in addition to acute care visits. Hence, we diagnosed, performed clinical measurements and collected comprehensive exposure information from several time-points during early childhood. The enrolment period was between March 2009 and November 2010 and with clinical follow-up of the children until March 2017.

Infection episodes

The children were monitored with daily diary cards during the first 3 years with parental registrations of any symptoms of cold (upper respiratory tract infection symptoms), gastroenteritis (diarrhoea or vomiting symptoms), any fever (>38°C) and doctor diagnosed acute otitis media, tonsillitis and pneumonia. The diary cards and diagnoses were reviewed with the families by the COPSAC physicians during the clinical visits to validate the symptom and disease entries. All episodes were entered into the database and double-checked.

Asthma

Asthma by age 6 years was diagnosed according to a previously validated algorithm¹⁰ requiring: (1) recurrent wheeze, (2) typical asthma symptoms, (3) need for short-acting inhaled beta2-agonist and (4) response to a 3-month trial of inhaled corticosteroids with relapse on cessation and was based on 12 clinical scheduled visits and acute visits until age 6 years.

Urbanicity gradient

We used birth addresses to translate into coordinates using Google API services and using the land cover database CORINE from 2012 for an unbiased definition of living environment.⁷ Land cover types around each coordinate were extracted from the CORINE2012 raster map (100 m resolution) with a 3 km buffer and quantified for each child as the proportions of 100 m tiles within the buffer area classified as each of the five major land cover types ((1) artificial surfaces; (2) agricultural areas; (3) forest and semi-natural areas; (4) wetlands; (5) water bodies). Next, a correlation matrix of proportions of five major land cover types within the buffer region was analysed by using principal component analysis (PCA). The first axis explained 44% of the variation and extracted to represent a gradient of urbanisation running from rural to urban environments. The PCA scores were clustered in a data-driven manner using partitioning around medoids clustering, which yielded two classes corresponding to an urban or a rural environment. Further details can be seen in our previous publication describing the same data.⁷

Covariates

We previously demonstrated several lifestyle related differences between children who lived in an urban versus rural environment such as exposure to furred pets during the first year, maternal education and income, time to daycare start and number of older siblings.⁷ In addition, we considered that the embedded fish oil and vitamin D interventions in pregnancy (2×2 factorial designed trial of 2.4 g/day n–3 LCPUFA versus placebo and 2800 IU/day versus 400 IU/day of vitamin D; NCT00798226 and NCT00856947), gestational age,¹¹ alcohol use,¹² antibiotic use¹³ and smoking during pregnancy,¹⁴ delivery mode,¹⁵ birth season,¹⁶ prenatal air pollution (particulate matter with diameters of ≤2.5 µm (PM_{2.5}),¹⁷

child hospitalisation at birth and genetic risk single nucleotide polymorphisms (SNPs) of FUT2 (rs504963, rs601338), CDHR3 (rs6967330) and 17q21 (rs2290400, rs7216389, rs9303277) that have previously been associated with common childhood infections^{18–21} could influence our results and therefore included these in our analyses as potential confounders. See online supplemental methods for further details on covariates.

Mechanistic data layers

Untargeted plasma metabolomics profiling of the mothers at week 24 was performed by Metabolon (NC, USA) using their HD4 liquid chromatography-mass spectrometry (LC-MS)/MS platform as previously described.²² Further, dried blood spot (DBS) samples were collected from the baby's heel 2–3 days after birth as part of the national newborn screening programme for inborn errors of metabolism and used for metabolomics profiling with LC-MS as previously described in detail.^{23,24}

The airway immune profile was assessed by measuring unstimulated levels of cytokines and chemokines in airway mucosal lining fluid sampled at age 1 month as described previously in details.^{7,25} The samples were collected with a pair of 3×15 mm strips of filter paper (Accuwik Ultra; fibrous hydroxylated polyester sheets, cat no. SPR0730, Pall Life Sciences, Portsmouth, Hampshire, UK) inserted into the anterior part of the inferior nasal turbinate of both nostrils. The strips were left for 2 min and after removal, the papers were frozen at –80°C and stored until analysis. The immune mediator panel was selected a priori to represent different types of immune responses including type 1, type 2, type 17 and Treg responses. The 20 cytokines and chemokines included interleukin (IL)-12p70, CXCL10, interferon (IFN)-γ, tumour necrosis factor (TNF)-α, CCL4, CCL2, CCL13, IL-4, IL-5, IL-13, CCL11, CCL26, CCL17, CCL22, IL-17, IL-1β, CXCL8, transforming growth factor (TGF)-β1, IL-10 and IL-2. The levels of these were determined by using high-sensitivity immunoassays based on electrochemiluminescence in a multiplex setting. The airway fluid samples were read in duplicated by using the Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, MD).

Airway microbiota samples were collected at ages 1 week, and 1 and 3 months with a soft catheter passed through the nose to the hypopharyngeal region. Gut microbiota samples were collected at age 1 week, 1 month and 1 year, where sampling was carried out at the COPSAC clinic or at home following detailed instructions. A full description of the laboratory workflow has been described previously.²⁶ Further details on the mechanistic data layers are described in online supplemental methods.

Statistical analysis

We analysed the risk of infection episodes between urban and rural environments using a Quasi-Poisson regression model adjusted for observation time estimating the incidence rate ratio (IRR). We also performed infection risk analyses using the gradient of urbanisation running from rural to urban environments as defined above as exposure.

When analysing the total number of infection episodes, we clustered each infection episode together as a sum of all episodes lasting at least 3 days with a minimum of 3 days between each episode. The adjusted analyses included all covariates described above and when analysing air pollution versus risk of infections, we additionally added urbanicity status as a covariate. Analyses of interactions were done by adding cross products to the Quasi-Poisson regression models.

We performed a PCA to capture the overall trend in the airway immune profile at age 4 weeks (concentrations were standardised, total sum normalised per sample, log transformed and z-scored before further analysis) and used a linear regression model to investigate association between urban living and principal component 1 (PC1) and PC2 and the associations with risk of infections. We used a sparse partial least squares (sPLS) model^{27,28} to create cross-validated blood metabolomic profile scores ('fingerprints') reflecting the metabolomic changes most associated with living environment in each sample, by extracting the cross-validated

predictions and combining them across folds into a single static continuous score used further in downstream analysis. See online supplemental methods for more details. This fingerprint was then investigated for associations with risk of infections as a normal continuous covariate, using Quasi-Poisson regression as described above. Thereafter, we performed a causal mediation analysis to investigate whether the effect of urban living on the risk of infections was mediated by the early airway immune profile or the maternal or child metabolomics profiles. Mediation was quantified as the average causal mediation effect (ACME). Finally, we analysed the risk of asthma by age 6 years from infection status using logistic regression and whether the link between urban living and asthma risk was mediated by infection load.

All analyses were performed with R software (V.4.0.3; R Foundation for Statistical Computing, Vienna, Austria). P values less than 0.05 were considered statistically significant as we have one overall hypothesis, that is, living environment versus infection risk and one main outcome that is, total number of infections and then analyse subtypes of infections related to the main outcome.

RESULTS

In the COPSAC2010 cohort, 663 children had available infection diary data and we observed a mean (SD) of 16.3 (8.4) of total number of infection episodes including cold, gastroenteritis, acute otitis media, pneumonia, tonsillitis or fever episodes until 3 years of age (online supplemental eFigure 1). The most frequent type of infection was cold with a mean of 12.2 (8.1) episodes per child (online supplemental eTable 1). Children who lived in an urban versus rural environment at birth were born to mothers with a higher education and income and an alcohol intake during pregnancy, had a later daycare start and had fewer older siblings (online supplemental eTable 1).

Urbanicity and risk of infections

We found that children living in an urban environment (n=360) were more susceptible to infections aged 0–3 years compared with children from a rural environment (n=289): mean total number of infections (SD) 17.1 (8.7) versus 15.2 (7.9), IRR (95% CI); 1.12 (1.04–1.20), p=0.003. This difference was also significant after adjustment for all the potential confounders, adjusted IRR (aIRR): 1.15 (1.05–1.26), p=0.002 (figure 1). When analysing individual infection types, cold and gastroenteritis episodes were more pronounced among children from an urban versus rural environment, although only the risk of cold remained statistically significant after adjustments: 1.21 (1.07–1.37), p=0.002 (figure 1). When using the

gradient of urbanisation (PC score) as exposure, we found that each increase per unit was associated with higher risk of both total number of infections and cold episodes (online supplemental eTable 3). In a stratified analysis excluding the 24 children whose living environments changed during the first year, we found even stronger associations for risk of both total number of infections: aIRR; 1.17 (1.07–1.29), p<0.001 and colds: 1.23 (1.09–1.40), p<0.001.

Air pollution

There was a strong association between urbanicity and exposure to air pollution (PM_{2.5}) in pregnancy from a linear regression model (p<0.001). Prenatal air pollution itself was not associated with the risk of total number of infections age 0–3 years when adjusted for potential confounders including urbanicity in a Quasi-Poisson regression model: aIRR; 0.94 (0.87–1.02), p=0.162. Further, there was no evidence of interaction between urbanicity and PM_{2.5} when investigating the association with infections (all p_{interactions}>0.05) (online supplemental eTable 4).

Genetics

We investigated the relationship between urbanicity and distribution of genetic risk SNPs and found no such relationship (all p>0.05). Further, there was no evidence of interaction between urbanicity and the genetic risk SNPs (all p_{interactions}>0.05) (online supplemental eTable 5).

Airway immune profile

We previously illustrated significant associations between urbanicity and the individual airway immune mediators at age 4 weeks in our cohort.⁷ Here, we found a significantly different overall airway immune profile at age 4 weeks in children born in an urban versus rural environment with the PC1 (p=0.012) and PC2 (p<0.001) explaining 17.6% and 12.7% of the variance, respectively (figure 2) where urban children had higher scores of both PC1 and PC2 compared with children from a rural environment. PC1 reflected a pattern related to perturbation of IL-1β (type 17), TNF-α (type 1), IL-13 (type 2), IL-10 (Treg) and CXCL8 (type 17) versus CCL17 (type 2), CCL11 (type 2) and CCL2 (type 1). PC2 reflected a pattern related to perturbation of IL-4 (type 2), CCL22 (type 2), CCL26 (type 2), IFN-γ (type 1) versus CCL4 (type 1), CXCL8 (type 17), TGF-β1 (Treg), CCL2 (type 1) and CCL11 (type 2). The PC scores indicated a more rural airway immune profile to be associated with higher concentrations of, for example, IL-10 (Treg) known to hold anti-inflammatory properties and hinder host response to microbial pathogenesis. The relationship between li-

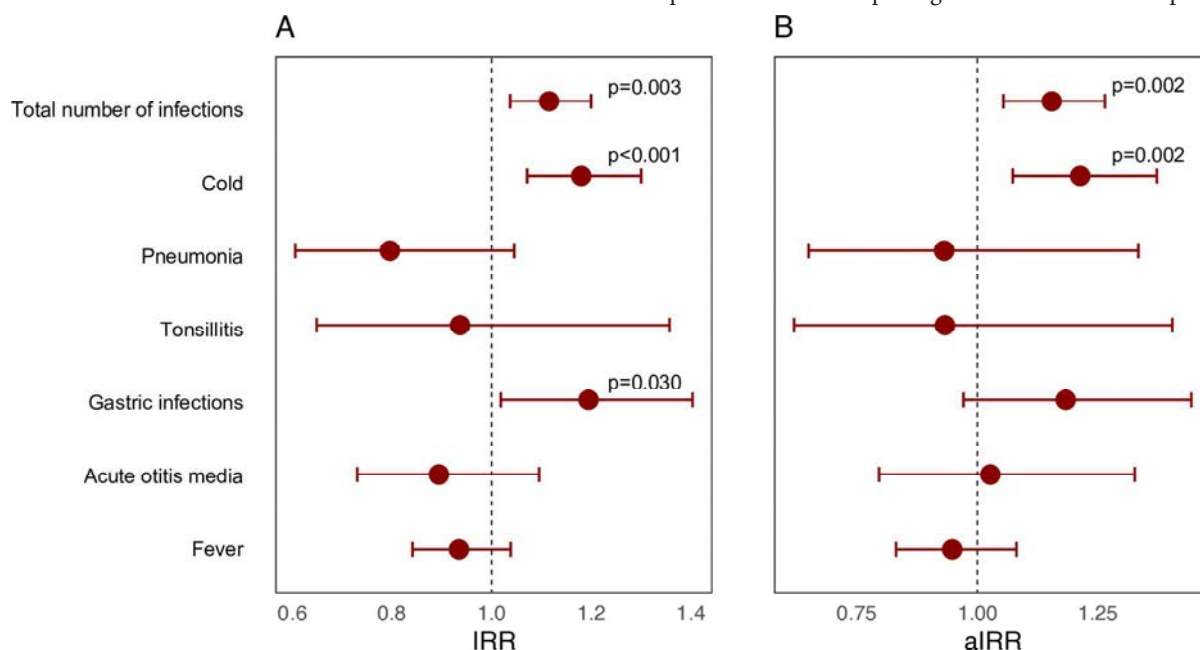


Figure 1 Urban versus rural living environment and risk of infections age 0–3 years in the COPSAC₂₀₁₀ cohort. (A) Quasi-Poisson regression analyses crude. (B) Quasi-Poisson regression analyses adjusted. aIRR, adjusted incidence rate ratio; IRR, incidence rate ratio.

ving environment and each cytokine and chemokine measured has been reported for our cohort in a recent publication also discussing the relation with the measured airway microbiota profiles and in relation to asthma.⁷ In this study, we found that the PC scores were positively related to the risk of total number of infections, PC1: aIRR; 1.03 (1.00–1.06), $p=0.038$ and PC2: 1.04 (1.01–1.07), $p=0.022$ (figure 3), where PC2 showed evidence of mediating the effect of urbanicity on risk of total number of infections: 17% effect mediated, adjusted $p_{ACME}=0.042$, but not PC1: adjusted $p_{ACME}=0.234$. In a stratified model only including children from a rural environment, we found similar associations between the PC scores and risk of total number of infections: PC1; 1.04 (1.00–1.08), $p=0.037$ and PC2; 1.05 (1.00–1.10), $p=0.05$.

Maternal and child metabolomic profiles

To explore the associations between urbanicity and the maternal week 24 and newborn DBS metabolomic profiles and how these were related to the risk of infections, we used supervised multivariate analysis, sPLS, to generate metabolomic fingerprints of urbanicity (figure 4 and online supplemental eFigure 2). We found that a component with a single metabolite yielded a high AUC (>0.8) and that adding a second (128 metabolites) and third (1 metabolite) component yielded slight but consistent improvements (figure 4A). The cross-validated predictions from the final model (urban maternal metabolomic fingerprint) were strongly associated with urbanicity (area under the curve (AUC) 0.86, OR 8.14 (6.00–11.39), $p=7.57e-38$, figure 4B). For the child metabolomic

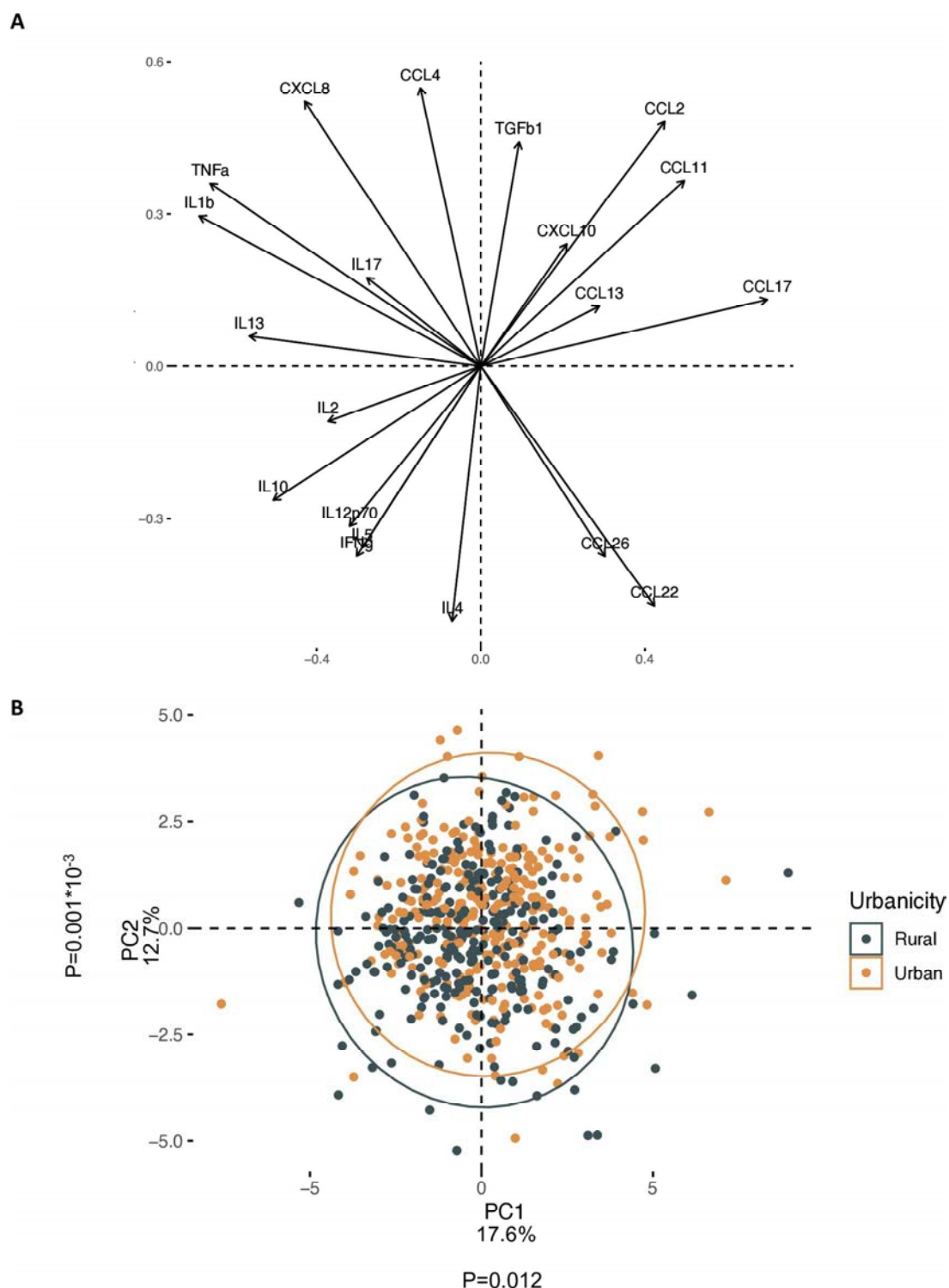


Figure 2 PCA loading (A) and score (B) plots of the airway immune profile at age 4 weeks showing patterns of correlation between immune mediators and the distribution of children according to immune profile stratified by urbanicity status. P values are from linear regression models of urbanicity status versus PC scores. PC1, principal component 1; PC2, principal component 2; PCA, principal component analysis.

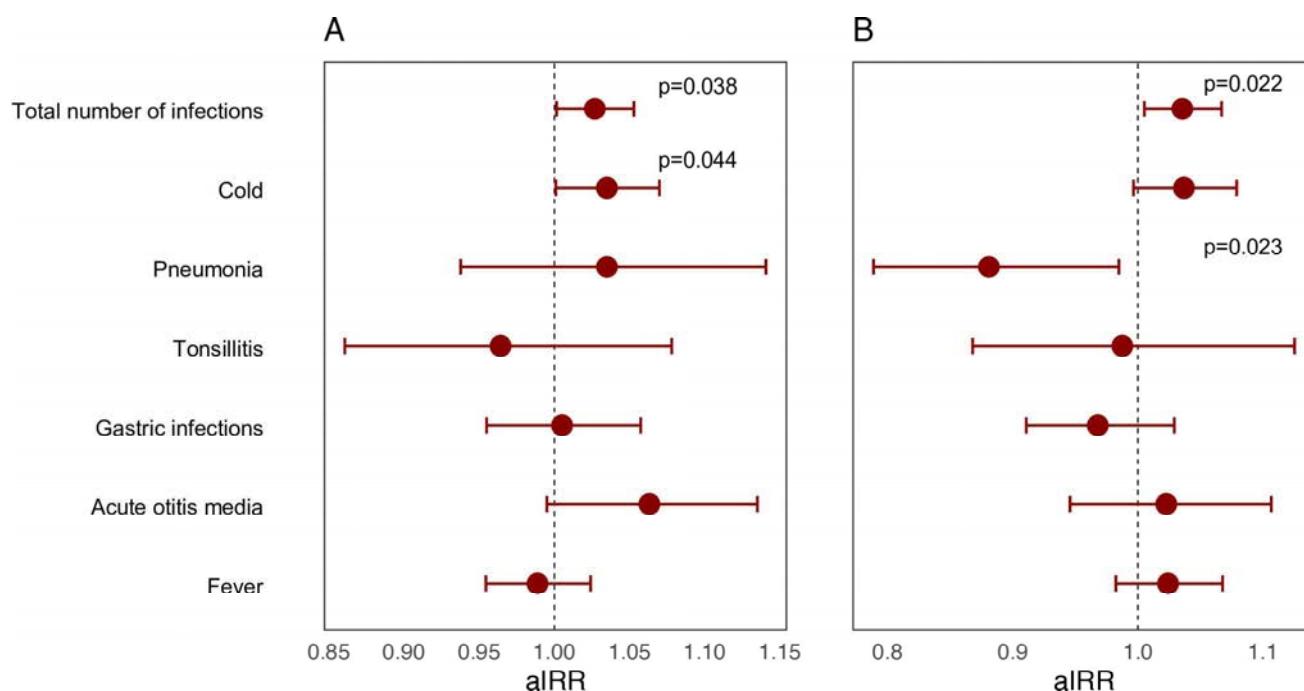


Figure 3 Airway immune profile principal component 1 (PC1) and PC2 versus risk of infections age 0–3 years in the COPSAC₂₀₁₀ cohort from adjusted Quasi-Poisson regression models. (A) PC1. (B) PC2. aIRR, adjusted incidence rate ratio.

fingerprint, we used a similar approach which yielded a 1-component model and showed a strong association with urbanicity as well (AUC 0.75, OR 2.80 (2.26–3.51), $p=3.85e-20$, online supplemental eFigure 2B).

The urban maternal metabolomic fingerprint was related to a higher risk of total number of infections: aIRR; 1.26 (1.09–1.44), $p=0.001$, whereas the urban child metabolomic fingerprint was related to a borderline higher risk: 1.33 (0.99–1.82), $p=0.065$, but significantly related to a higher risk of cold episodes: 1.77 (1.17–2.70), $p=0.008$ (figure 5). Further, we analysed these associations in a stratified model only including children from a rural living environment and found similar results for the maternal metabolomic fingerprint: aIRR, total number of infections; 1.31 (1.06–1.61), $p=0.01$, but not the child metabolomic fingerprint: 1.18 (0.77–1.81), $p=0.45$. The effects of urbanicity on risk of total number of infections and cold episodes were borderline mediated through the maternal metabolomic fingerprint: 41% effect mediated, adjusted $p_{ACME}=0.074$ and 44% effect mediated, adjusted $p_{ACME}=0.052$, respectively. The child metabolomic fingerprint did not mediate the effect of urbanicity on risk of total number of infections: adjusted $p_{ACME}=0.346$ but a borderline mediation effect on risk of cold was observed: 25% effect mediated, adjusted $p_{ACME}=0.076$. Interestingly, we found significant associations between the maternal metabolomic fingerprint and child airway immune profile scores (PC1; $p=0.007$ and PC2; $p<0.001$) as well as the child metabolomic fingerprint and child airway immune profile score for PC2 ($p<0.001$) but not PC1 ($p=0.63$).

In component 1 explaining the maternal pregnancy sPLS urbanicity metabolite model, the amino acid cysteine s-sulfate contributed alone, whereas in component 2 many metabolites with a characteristic enrichment of lipids with negative loadings and amino acids, nucleotides and peptides with positive loadings contributed to the model (see full metabolite list in online supplemental eTable 6) and in component 3 only the lipid hexadecadienoate contributed (figure 4C). After performing a pathway enrichment analysis of the metabolites in component 2 and after multiple test correction (Bonferroni), we found that the long-chained saturated and monounsaturated fatty acid sub-pathway showed significant enrichment, which did not include the n–3 and n–6 polyunsaturated fatty acids (online supplemental eFigure 3).

All the measured saturated and unsaturated fatty acids were higher in mothers living rural versus urban (online supplemental eTable 7) with palmitate (palmitic acid) as the most pronounced,

which was associated with a decreased risk of childhood infections: aIRR; 0.89 (0.80–0.99), $p=0.039$. We also found the amino acid cysteine s-sulfate from component 1 that was elevated in rural mothers to be associated with a decreased risk of infections: 0.90 (0.84–0.97), $p=0.003$. In component 1 explaining the child DBS sPLS urbanicity metabolite model, two annotated metabolites didecyldimethylammonium (disinfectant liquid) and 2,4,7,9-tetramethyl-5-decyne-4,7-diol (cleaning chemical) and two unannotated metabolites contributed to the model. In an attempt to clarify these two unannotated metabolites, we investigated their correlations (Pearson) with other DBS metabolites ($n_{\text{metabolites}}=2305$) but did not find them to be strongly correlated ($R>0.70$) with any from the list of annotated metabolites in our DBS sample dataset, thus not revealing any pathway relationships.

Airway immune profile

We previously illustrated significant associations between urbanicity and the individual airway immune mediators at age 4 weeks in our cohort.⁷

Child airway and gut microbiome profiles

As we previously performed an sPLS model to create bacterial fingerprints of the airways (age 1 week, 1 month and 3 months) and the gut microbiome (age 1 week, 1 month and 1 year) of the child from urbanicity status,⁷ we used these to investigate a possible relation between the urbanised microbiota and risk of infection outcomes. This showed that the urbanised airway microbiome profile at age 3 months was associated with a higher risk of tonsillitis episodes: IRR; 1.32 (1.09–1.62), $p=0.006$, whereas the airway profile at age 1 week and 1 month and gut profile at any time point were not significantly associated with any of the infection outcomes including respiratory and gastric infections ($p>0.05$) (online supplemental eTable 8). As there was no association between urbanicity and risk of tonsillitis we did not perform a mediation analysis.

Urbanicity, infections and risk of asthma by age 6 years

We investigated the relationship between urbanicity, infections in early life and later risk of asthma by age 6 years as we previously demonstrated a link between urbanicity and risk of childhood asthma.⁷ From an adjusted logistic regression model, we found that urbanicity was associated with a higher risk of developing asthma by age 6 years: adjusted OR: 2.39 (1.43–4.10), $p=0.001$. We also found that for each infection episode at age 0–3 years the risk

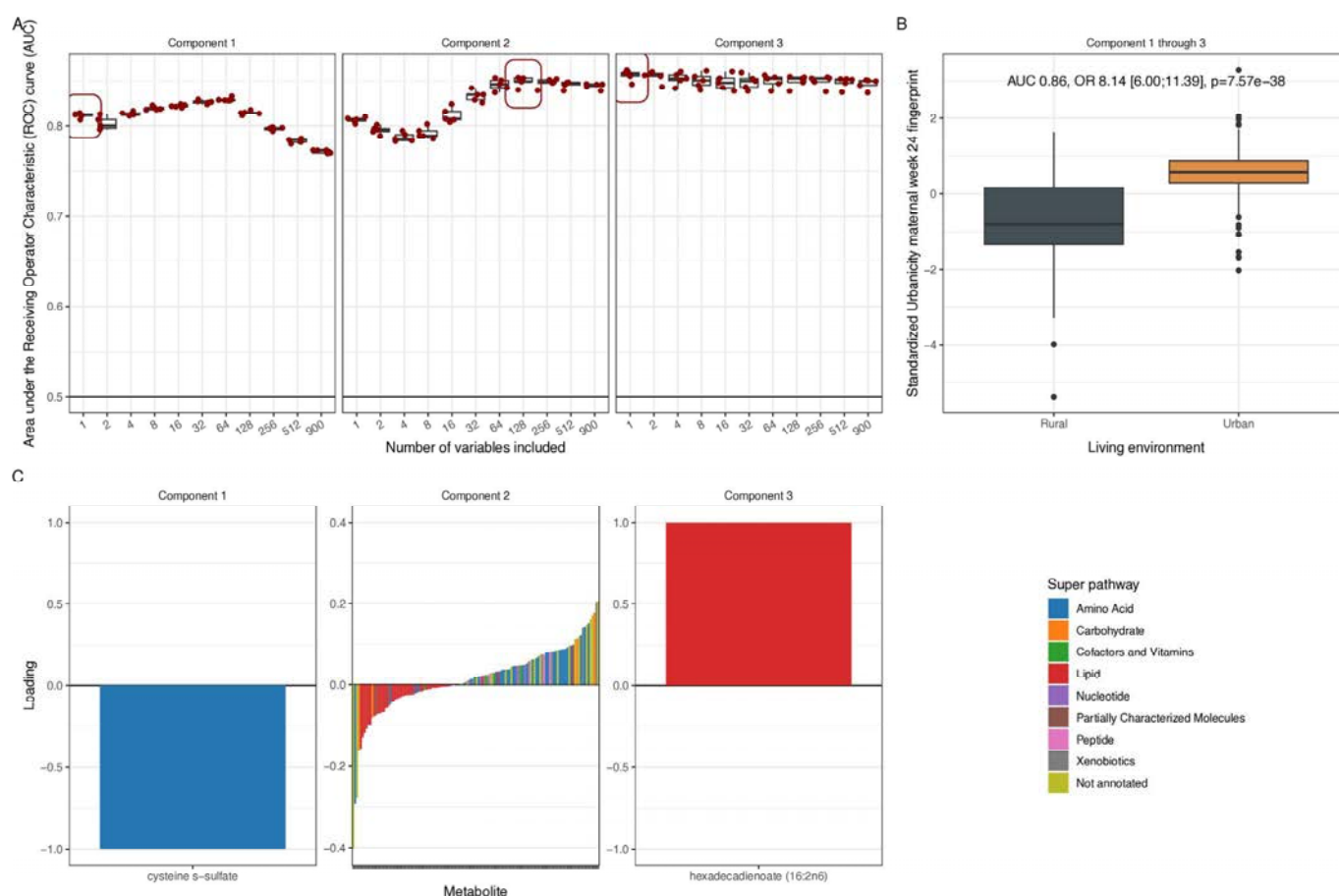


Figure 4 Sparse partial least squares model predicting urban versus rural living environment from maternal pregnancy week 24 plasma metabolome profiles. (A) Cross-validation plot showing maximum area under the curve (AUC) values, sequentially selecting number of variables per component by restricting the model to only include 1 metabolite on component 1, 128 metabolites on component 2 and 1 metabolite on component 3. Each dot represents a repeated cross-validation per parameter set. (B) The cross-validated predictions from the median performing model with three components (A) were standardised with Z-scaling strongly associated with living environment. (C) Overview of selected metabolites. Components 1 and 3 only had one selected metabolite; for component 1, an amino acid (cysteine s-sulfate) was selected, while for component 3 a lipid (hexadecadienoate) was selected. Component 2 was composed of many metabolites with a characteristic enrichment of lipids with negative loadings and amino acids, nucleotides and peptides with positive loadings.

increased for developing asthma by age 6 years: 1.15 (1.11–1.19), $p < 0.001$. Finally, a causal mediation analysis revealed mediation through infections age 0–3 years when analysing urbanicity versus risk of asthma by age 6 years: 36% effect mediated, adjusted $pACME < 0.001$ (overview in figure 6).

DISCUSSION

In the Danish population-based COPSAC2010 mother–child cohort, we found that urbanisation at birth reflecting the prenatal and postnatal living environment was associated with an overall increased infection burden driven by colds during the first 3 years of life. An urban airway immune profile in the children at age 4 weeks and urban metabolomic profiles in the mothers during pregnancy and in the children at birth were associated with a higher risk of infections, which explained some of the association between urbanicity and infection load. In contrast, the urban child airway and gut microbiota were not associated with an overall risk of infections. Adjusted analyses suggested that these associations were independent of potential confounding factors such as social circumstances, air pollution, genetic risk profiles and several other environmental exposures before and around birth. Finally, we found an association between infection load in early childhood and risk of asthma by age 6 years and that the previously established association between urban living and risk of asthma was mediated through this increased infection load.

Interpretation

Infections in early childhood and in particular respiratory infections are associated with high morbidity and mortality globally,

which has led to a recent (2020) large study investigating potential risk factors among children younger than 5 years,²⁹ but without investigating the effect of urbanicity. A smaller previous questionnaire study found an increased prevalence of respiratory infections among preschool aged children from urban versus rural areas, and despite that such a study design is prone to recall bias it is in line with our findings.³⁰ Another study among 2510 school-children, showed that a rural to urban migration was associated with an increased risk of childhood wheezing episodes.³¹ Although these studies support our main results none of them investigated potential underlying mechanisms. To our knowledge, we are the first large longitudinal cohort study to report urban changes in the child airway immune profile and maternal and child blood metabolomic profiles that are linked to risk of childhood infections.

The hypothesised prenatal and neonatal windows of opportunity are considered critical time frames in a child's life for lifelong health.³² During this period, environmental factors seem highly important for optimal immune maturation, which is emphasised by our results suggesting living environment as a determinant for airway immune mediator levels and blood metabolic profiles that may influence immune function during childhood. Our findings did not suggest the urban changes measured in the airway and gut microbiota to be of importance for infection proneness in early childhood in contrast to our previous findings on asthma,⁷ which was a bit surprising given that symptoms of asthma in early childhood are often triggered by airway infections. These findings suggest different underlying mechanisms to explain the associations between a perinatal urban living environment and later risk of childhood infections and asthma, respectively. Instead, we found

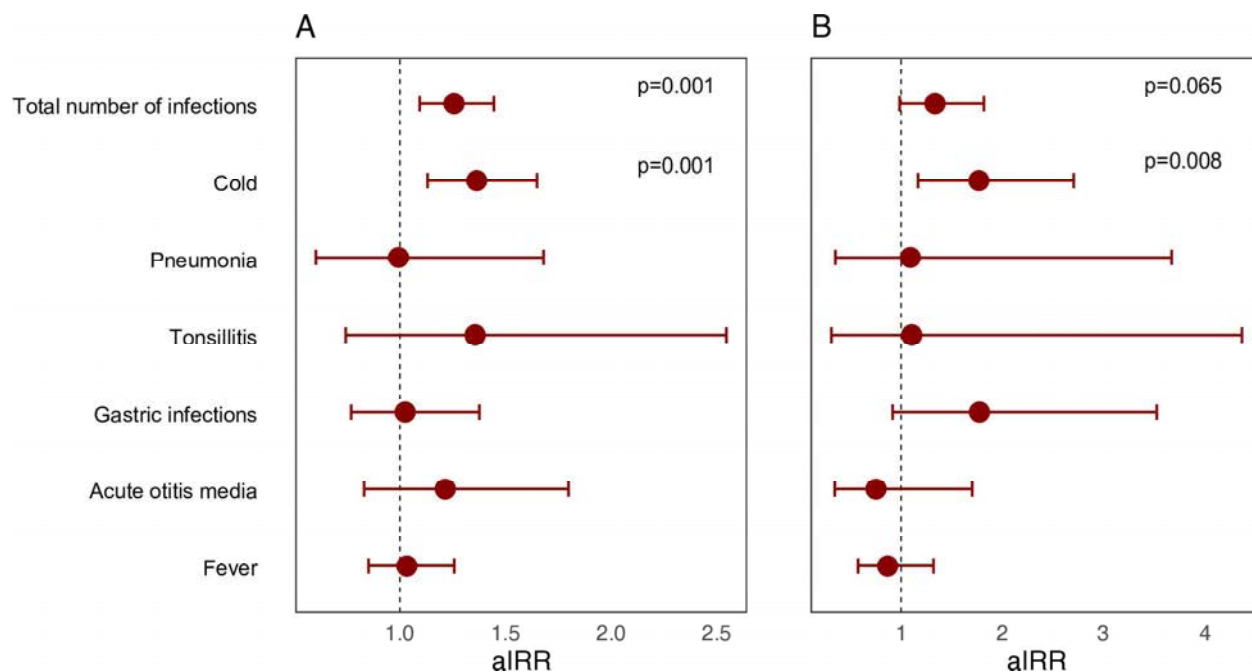


Figure 5 Maternal week 24 and neonatal dry blood spot age 2–3 days urbanicity metabolomic profiles from sparse partial least squares models versus risk of infections age 0–3 years in the COPSAC₂₀₁₀ cohort from adjusted Quasi-Poisson regression models. (A) Maternal pregnancy profile. (B) Neonatal dry blood spot profile. aIRR, adjusted incidence rate ratio.

strong evidence of mediation from the infection burden early in life for the effect of urbanicity on later asthma risk, which adds to our previous study.

Dietary intake during pregnancy has been suggested to play a key role for disease in offspring as previously shown^{33–35} and since we found changes in metabolic pathways associated with maternal diet, we hypothesised that this might explain the protective effect of rural versus urban living during pregnancy on childhood infection load. We found that the metabolite levels measured at pregnancy week 24 of long-chained saturated and monounsaturated fatty acids were all elevated in mothers living rural versus urban. Interestingly, a recent experimental study (2022) demonstrated that saturated fatty acids, and in particular palmitic acid, which was elevated in our rural mothers, acted as primary stimuli to induce trained immunity through a hyper-inflammatory response, which enhances the clearance of infections.³⁶ This path of trained immunity went through changes in the innate immune response and the authors suggested that the saturated fat acted as a brief pulse of inflammation that alters the later immune cell production in a favourable way for protection against pathogens. In addition, they found that a diet high in saturated fatty acids changed the inflammatory cytokine profile, which could explain our findings of changes in the children's early airway immunology profile at only 4 weeks of age as a result of pregnancy dietary habits. On the other hand, saturated fatty acids were in the same study linked to a higher risk of sepsis making it a strict balance between healthy versus non-healthy properties. Furthermore, antimicrobial and antifungal activity have been associated with saturated fatty acids in a recent review.³⁷ This supports the hypothesis that maternal diet could play a crucial role in the child's developing immune system during the early critical prenatal developmental period in pregnancy.

Interestingly, the increased risk of infections by urbanicity was not only restricted to colds as we observed an increased risk for gastroenteritis episodes in our unadjusted analyses suggesting a multiple organ effect, although when adjusting for multiple potential confounders this association disappeared. There was no association between urbanicity and risk of pneumonia, but this could be due to the fewer number of pneumonia episodes compared with cold episodes reducing the statistical power.

Finally, we found a link between urbanicity, infection burden and later risk of asthma by age 6 years. The link between colds, which were the dominating infection type in our study, and later asthma risk has recently (2022) been demonstrated in a large Eu-

ropean meta-analysis investigating the influence of infections between age 6 months and 5 years on later asthma risk until age 15 years among 150 000 children suggesting early-life upper respiratory infections to be a significant risk factor for asthma⁴ supporting our findings.

Strengths and limitations

The study was strengthened by the close longitudinal follow-up and daily registration of infection episodes from birth until age 3 years in combination with the comprehensive amount of information on environmental exposures and mechanistic data layers, including the early child airway immune profile, blood metabolomics from both the mother and child, genetic profiles and airway and gut microbiota at several timepoints. This allows for deep clinical phenotyping of the children through early childhood and adjustment for several potential confounders that could influence our findings allowing for a thorough assessment of the association between urbanicity and disease development. Finally, the study was strengthened by the population-based design including Danish pregnant women that allows for generalisation of our findings. However, this is an observational study with the risk of residual confounding that does not allow for drawing causal conclusions. Numerous factors differ between urban and rural children⁷ other than those adjusted for such as type and size of daycare, size of home and indoor versus outdoor activities that could all increase the infection burden. In our analyses, we adjusted for all relevant and available exposome data on the mothers and children in the cohort reflecting both lifestyle and genetic predisposition that could influence the risk of infections. Hence, we interpret the association between urbanicity and infection risk to be something else than these factors, which also included exposure to air pollution, and we can only speculate what might increase the risk in children born in an urban environment and what is being proxied by the exposure. In our study, children who lived in an urban versus rural environment at birth were born to mothers with a higher education and income and an alcohol intake during pregnancy, had a later daycare start and had fewer older siblings, but these differences were most likely not explaining the association between living environment and infection risk as we adjusted our analyses for these and other potential confounders. Further studies investigating the differences between urban versus rural living including even more data layers covering lifestyle and environmental exposures are warranted in the future to specifically target these areas already during pregnancy as we observed maternal and newborn

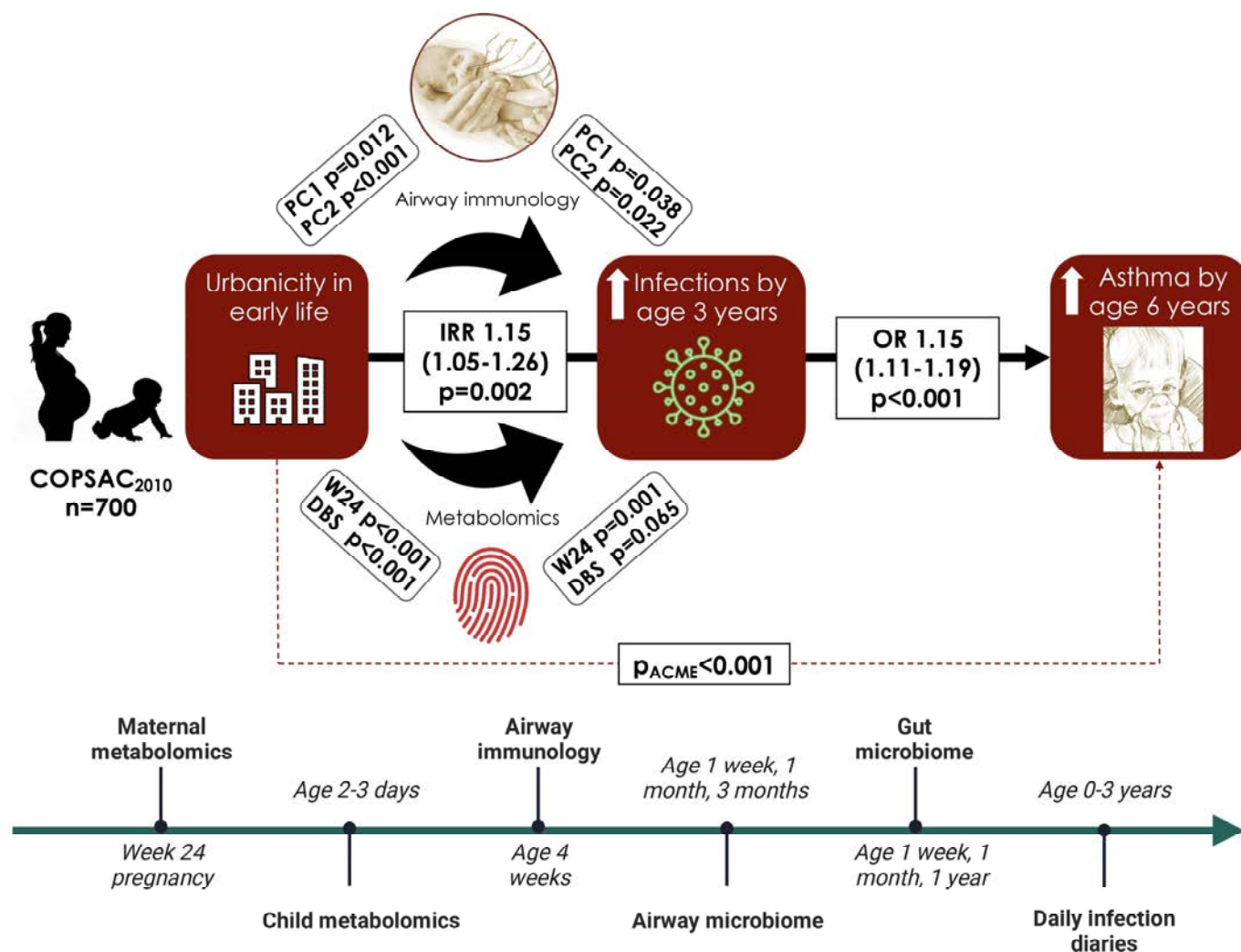


Figure 6 Overview figure of the main measurements and findings of the study. DBS, dried blood spot; PC1, principal component 1; PC2, principal component 2.

changes to have an impact on later disease development. Such studies could have the potential to reveal what the urbanisation proxy used in this study actually reflects in the search for a protective preventive strategy against early-life infections. Our findings showing changes in the pregnancy maternal and newborn child blood metabolomic profiles as well as the early child airway immune profile point towards early life factors rather than urban versus rural differences throughout childhood such as daycare and outdoor activities. Finally, the relatively small effect sizes on risk of infections observed among urban versus rural children might be due to an underestimation from the two-level grouping derived from the gradient of urbanisation. When analysing the urbanicity exposure as a continuous score, we found even larger effect sizes supporting this argument.

CONCLUSIONS

This study demonstrated association between an urban living environment at birth and an increased load of common infections in early childhood, which was explained through changes in the early airway immune profile of the children and blood metabolic profiles of the pregnant mothers and newborn children. However, the factors causing these changes as reflected by living environment are still unknown and further studies are needed. In addition, the previously demonstrated association between urban living and risk of childhood asthma was found to be mediated through an increased infection load early in childhood.

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Relação entre a exposição cumulativa à sílica e a silicose: uma revisão sistemática e uma meta-análise dose-resposta

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RESUMO

Contexto A silicose, uma doença respiratória crônica causada pela exposição à sílica cristalina, é um problema persistente de saúde pulmonar a nível mundial. Não existe uma revisão sistemática da relação entre a exposição cumulativa à sílica cristalina respirável (SCR) e a silicose. Os limites de exposição no Reino Unido estão atualmente a ser revistos. Por conseguinte, realizámos uma revisão sistemática e uma meta-análise da relação dose-resposta desta relação.

Métodos A 24 de fevereiro de 2023, foram pesquisadas a Web of Science, a Medline e a Embase. Foram incluídos estudos de silicose radiográfica, autópsia ou certidão de óbito, com um acompanhamento médio estimado de mais de 20 anos desde o primeiro emprego. Foram comparados os métodos de risco cumulativo de silicose. Os riscos relativos (RR) da silicose em exposições cumulativas crescentes foram calculados e utilizados para estimar a redução de risco absoluto (RRA).

Resultados Oito estudos elegíveis, incluindo 10 coortes, contribuíram com 8792 casos de silicose entre 65 977 participantes. Existem diferenças substanciais nas estimativas de risco cumulativo entre metodologias. Utilizando o mesmo método, observámos riscos cumulativos de silicose mais elevados nas coortes mineiras do que nas coortes não mineiras. Uma redução de 4 para 2 mg/m³-ano na exposição cumulativa a SCR correspondeu a reduções substanciais do risco entre os mineiros [RR 0,23 (95% IC 0,18 a 0,29, I²=92,9%) com uma RRA de 323 (95% IC 298 a 344) por 1000] e não mineiros [RR 0,55 (95% IC 0,36 a 0,83, I²=77,0%) com uma RRA de 23 (95% IC 9 a 33) por 1000].

Conclusão Apesar da heterogeneidade significativa, os nossos resultados apoiam uma redução dos limites de exposição admissíveis de 0,1 mg/m³ para 0,05 mg/m³, particularmente entre as populações mineiras. É necessária mais investigação entre as populações não mineiras, uma vez que apenas dois estudos foram elegíveis.

INTRODUCTION

The forthcoming High-Level Meeting of the United Nations General Assembly on Non-Communicable Diseases (NCDs) will address the 15 million premature deaths from NCDs annually, most of which occur in low-income and middle-income countries (LMICs).¹ The United Nations Sustainable Development Goals (SDGs) demand 'safe, effective, quality and affordable essential medicines for all' by 2030.² Non-communicable chronic respiratory diseases (CRDs), for example, asthma and chronic obstructive pulmonary disease (COPD), cause substantial morbidity and mortality, disproportionately affecting those living in poverty in LMICs.³ Recommended medicines for CRDs include inhaled and oral drugs that are on the WHO Model List of Essential Medicines (EML), which defines safe, efficacious, cost-effective medicines that should be available everywhere.⁴ Access to essential, affordable CRD medicines is limited in LMICs.^{5,6} Up-to-date data on the availability, cost and affordability of WHO essential medicines for CRDs in LMICs are missing.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Despite decades of research, evidence regarding the relationship between cumulative respirable silica and silicosis has not been appraised in a systematic review process or quantified using meta-analysis methods.

WHAT THIS STUDY ADDS

► Using reproducible methods, we showed substantial differences in cumulative risk estimates of individual studies, dependent on which methodology was used. In a dose-response meta-analysis, we demonstrated clinically important reductions in silicosis risk at cumulative respirable silica thresholds relevant to UK and US policy debates. Silicosis risks appear different among miners than non-miners, although only two studies of non-miners were included.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► There is current debate regarding respirable crystalline silica exposure limits in the UK and recent debate among miners in the USA. This research supports the reduction of permissible exposure limits from 0.1 mg/m³ to 0.05 mg/m³. More studies of non-miners are needed.

BACKGROUND

Silicosis is an incurable respiratory disease caused by exposure to respirable crystalline silica (RCS). The global burden of silicosis is unclear; high prevalence among mining¹ and non-mining industries,² ongoing high exposures and concerns of under-reporting mean silicosis morbidity and mortality is likely far higher than modelled estimates.³ Chronic silicosis, the most common form, may present decades after lower dose exposures and is considered the primary outcome of this study. Acute and accelerated silicosis presents within 10 years of high intensity exposure. Lower grade silicosis may be asymptomatic, but disease progression after exposure cessation can occur with subsequent disabling dyspnoea and cough. Silica exposure is also associated, in a dose-response manner, with silicosis mortality, lung cancer, tuberculosis, autoimmune disease and renal disease.^{4,5}

Despite decades of research, permissible exposure limits (PELs)—representing average intensity of RCS exposure over an 8-hour working shift—

are debated and range from 0.05 (USA) to 0.35 mg/m³ (China).⁶ The most comprehensive review of silica exposure risks was the 2016 US Occupational Safety and Health Administration (OSHA) Federal ruling, resulting in reduction of the US PEL from 0.1 mg/m³ to 0.05 mg/m³.⁷ The OSHA's silicosis prevalence estimates were 60–773/1000 workers for 45-year exposures at an average exposure of 0.1 mg/m³ and 20–170/1000 workers for 45-year exposures at 0.05 mg/m³.⁷ The OSHA legislation excludes the US mining industry in which the PEL was reduced from 0.1 mg/m³ to 0.05 mg/m³ earlier in 2024.⁸ There is a current UK government call for evidence regarding this same reduction (0.1 mg/m³ to 0.05 mg/m³).⁹

The OSHA review findings should be interpreted cautiously. First, the review methods are not described. Second, the prevalence estimates used relied on respective study methods and in one case were estimated from graphs.¹⁰ Finally, the authors compared different outcomes—for example, modelled (instantaneous) odds of disease¹¹ and cumulative risk. The OSHA conclusions were similar to those of a prior review which stated that “30 years exposure at 0.1 mg/m³ might lead to a lifetime silicosis risk of about 25%, whereas reduction of the exposure to 0.05 mg/m³ might reduce the risk to under 5%”.¹² Both reviews noted between-study heterogeneity, partly explained by methodological differences. Conversely, plots comparing non-parametric cumulative risks demonstrate similarities between multiple selected studies.^{13 14}

A limitation of the above evidence is the use of non-systematic review methods to present narrative findings and, in some cases, non-transparent methods to provide quantitative summaries. Furthermore, no study has investigated the impact of different cumulative risk calculation methods used by included studies. An intrinsic limitation of using radiographic silicosis as an outcome is the presence of sub-radiological silicosis, even at higher autopsy and CT grades of disease.¹⁵ The recent development of a ‘dose-response meta-analysis’ enables the meta-analysis of relative risks of silicosis from different study methodologies (eg, case-control, cohort study) across RCS dose categories.¹⁶

We therefore aimed to investigate the relationship between cumulative RCS exposure and silicosis risk by (1) systematically reviewing studies in which adequate latency to achieve the outcome has been achieved; (2) using a life table approach to calculate the cumulative silicosis risk within reported exposure categories; and (3) performing a dose-response meta-analysis to quantify the relationship and heterogeneity between studies.

METHODS

Search strategy and selection criteria

This review follows the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) statement and was registered with PROSPERO (CRD42023401673). Studies indexed before 24 February 2023 were retrieved from Web of Science, Medline and Embase. Search strategies included terms for ‘silicosis’ and ‘cumulative exposure’ (see online supplemental file 1). All studies in previous reviews were captured by our searches.^{7 12} Selection criteria included English language studies of RCS-exposed adults, reporting an individual estimation of RCS and subsequent categorical dose ranges. Silicosis was defined by radiological diagnosis, using International Labour Organisation (ILO) classification or similar, or autopsy. We included studies where mean or median duration since starting work was estimated at >20 years; this represented a pragmatic balance of capturing the increased silicosis risk observed after 20 years^{10 17 18} while maintaining adequate study numbers.

Study selection and data extraction were performed on the Covidence platform (figure 1). Following de-duplication, two authors (JG, PH) independently screened abstracts and full texts, with conflicts resolved through final author review (JF). Contact with authors of studies with plausible population overlap was attempted but not successful. In these cases, we chose the study with the most detailed exposure categories.

Data analysis

Two authors (JG, PH) independently extracted study characteristics and performed quality assessment (see online supplemental file 2). Concentrations and categorical cumulative RCS or dust exposures were extracted. Where cumulative dust exposures were presented, we used the study's own reported conversion equation to estimate RCS.^{10 19} Study quality was assessed using an adapted version of the Newcastle–Ottawa Scale (NOS). We removed the NOS ‘comparability’ section as our relationship of interest was univariate; adjustment for confounding and effect was not relevant.

Data synthesis

For all studies we re-calculated the cumulative risk of silicosis by the SAS LIFETEST method used by Chen et al and Hnizdo and Sluis-Cremer,^{10 19 20} and the method used by Steenland and Brown¹⁴ (see online supplemental file 3). For dose ranges where the lower limit was missing, it was assumed zero. Where the upper limit was missing, it was assumed the highest category width was 1.5× greater

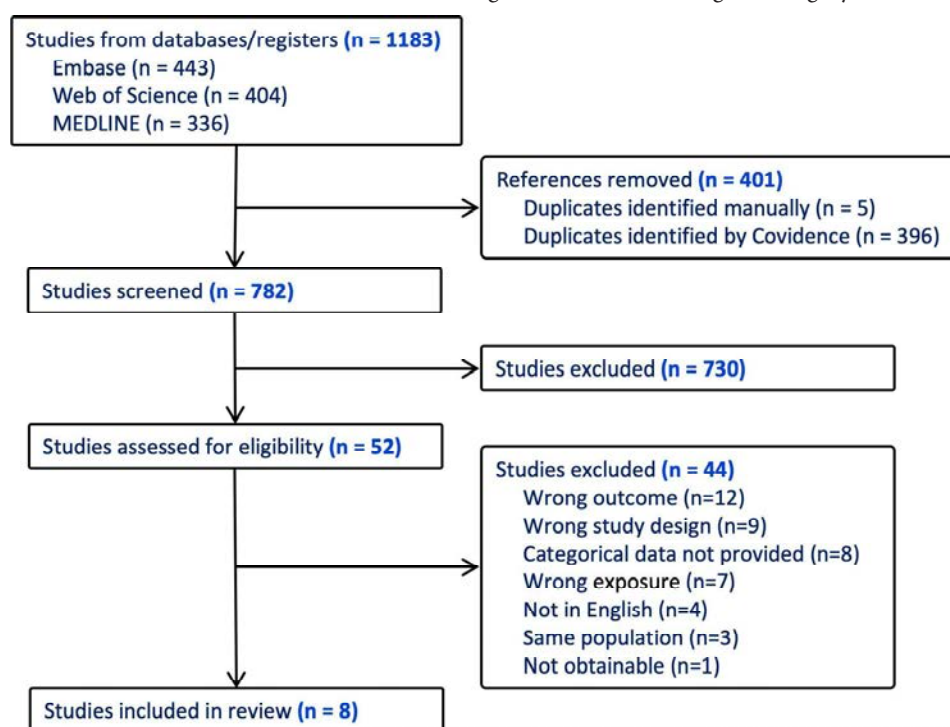


Figure 1 PRISMA diagram.

Table 1 Characteristics of the seven studies which fit the inclusion criteria

Authors, year of publication, industry, location	Study duration and follow-up since first exposure	Exposure measurement	Diagnostic classification	Silicosis cases/sample size; risk	Analysis methods	Mean silicosis latency (years)	Mean intensity (mg/m ³)	Loss to follow-up/censoring
Cross-sectional studies								
Hnizdo and Sluis-Cremer, 1993 Gold mines; South Africa ¹⁹	Employed ≥10 years 1968–1971. Subsequent annual radiograph; post-employment follow-up to mean 1982 (range 1968–1991) via 'occasional radiological examination'. Mean 24 years service (range 10–43)	Airborne shift dust sampling from 20 gold mines and 13 locations in mines by thermal precipitator and konimeter. Approximate silica content 30% ^{24,37}	ILO. Earliest radiograph ≥1/1 * Blind reading by three trained readers; one who correlated best with autopsy chosen	313/2235 (14%)	Cumulative risk – SAS PROC LIFETEST (Life table) Cumulative risk model – SAS PROC LIFEREG; Loglogistic	34.6	0.087	0/2235 (0%)
Steenland and Brown, 1995 Gold mines; USA ¹⁴	Employed ≥1 year underground 1940–1965. Follow-up to 1990 via death certificate and radiographs during two cross-sectional surveys in 1960 and 1976. Average follow-up 37 years, average employment 9 years	1153 personal air samples with cyclone-filter. Silica via infrared spectrometry ³⁸	ILO. Earliest radiograph ≥1/1 or 'small opacities' and death certificate. Unclear radiology method	170/3330 (5%) 128 cases by death certificate only, 29 by x-ray only, 13 by both	Cumulative risk – specified formula	Not reported	0.09 14% no data on exposure after 1975; possible underestimation	67/3330 (2%)
Hughes, <i>et al</i> 1998 Diatomaceous mine and processing; USA ²²	Employed >1 year 1942–1987. 'Periodic radiographs'. Median employment 5.5 years (range 1–49.3 years). Median follow-up 29.9 years (range 1–53 years) ³⁹	5174 airborne shift samples from particle impinger and gravimetric pump. Silica content (10–25%) estimated based on materials processed ^{39,40}	ILO. Earliest radiograph ≥1/0 or large opacities. At least 2 of 3 certified 'B' readers for +ve result	81/1809 (4.5%)	Cumulative risk – SAS PROC LIFETEST (Life table) Cumulative risk model – SAS PROC LIFEREG; Loglogistic	11.4	1452/1809 had mean exposure <0.5 mg/m ³ 357/1809 had mean exposure >0.5 mg/m ³	Unclear. 214/2342 (9%) 'unknown' at study end in 1994 ²⁹
Chen <i>et al</i> , 2005 Tin mines, tungsten mines, pottery factories; China ¹⁰	Started work after 1950, worked ≥1 year 1960–1974. Yearly radiographs since 1963. Follow-up to 1994. Minimum follow-up 26 years. Mean years of dust exposure pottery 24.9 years, tin 16.4 years, tungsten 16.5 years	Airborne gravimetric sampling from historical samples. Dust and silica content validated by side-by-side gravimetric sampling and X-ray diffraction	Chinese classification system. Earliest radiograph stage 1 or above. Agreement of 2 of 3 radiologists required	2816/14 427 (20%) tungsten miners, 855/4028 (21%) tin miners, 785/4547 (17%) pottery workers	Cumulative risk – SAS PROC LIFETEST (Life table) Cumulative risk model – SAS PROC LIFEREG; Weibull	Tungsten: 19.0 Tin: 20.2 Pottery: 29.4	Tungsten: 0.2 Tin: 0.152 Pottery: 0.254	Tungsten 82/9007 (0.9%) Tin: 12/4028 (3%) Pottery: 4/4547 (0.1%)
Liu <i>et al</i> , 2013 Metal mines, pottery factories; China ²⁵	Worked ≥1 year 1960–1974. All participants followed up to 2003 unless died or lost to follow-up. Yearly radiographs since 1963. Average follow-up 34.5 years	Airborne gravimetric sampling from historical samples. Dust and silica content validated by side-by-side gravimetric sampling and X-ray diffraction	Chinese classification system. Radiographs stage 1 or above. No radiology method reported	5297/34 018 (16%): ▲ 9007 tungsten miners ▲ 7663 iron miners ▲ 7348 pottery workers	No silicosis analytical methods	Not reported	Tungsten: 0.52 Iron: 0.08 Pottery: 0.15–0.30 (1960–1980), 0.12–0.15 (post 1990)	1527/34 018 (4.5%)
Cross-sectional studies								
Kreiss and Zhen, 1996 Hardrock mine; USA ¹⁸	Random sample of dust exposed, aged >40 years in mining town. Radiographs performed in 1984 or 1986. Mean time from first exposure 36.1 years, minimum 13 years	Airborne samples; 649 job title-specific gravimetric dust measurements and 484 silica measurements between 1974 and 1982	ILO. Median of three B readers; radiologic profusion of >1/0	32/100 (32%)	No cumulative risk. Modelling: logistic regression	Not reported	Silicotics: 0.08 Non-silicotics: 0.06	6/100 (6%) miners no exposure data

Continued

Table 1 Continued		Authors, year of publication, industry, location	Study duration and follow-up since first exposure	Exposure measurement	Diagnostic classification	Silicosis cases/sample size; risk	Analysis methods	Mean silicosis latency (years)	Mean intensity (mg/m ³)	Loss to follow-up/ censoring
		Miller <i>et al</i> , 1998 ¹¹ Coal mine; Scotland	Available radiographs from any years of 1970/1974/1978. Outcome based on follow-up radiograph in 1991. Minimum follow-up 13 years. Pit closure 1981	Regular (<yearly) airborne samples, initially thermal impinger then gravimetric pump. Silica via infrared spectrometry ⁴¹	ILO. Most recent radiograph ≥2/1. Median result of three 'experienced readers'	47/547 (9%)	No cumulative risk. Modelling: logistic regression	Not reported	Not reported	NA. However study is of 547/1416 (39%) traceable survivors
		Rosenman, <i>et al</i> 1996 Foundry; USA ²³	Employed ≥5 years before 1986; medical records up to 1991 used. Most recent radiographs obtained via work records or 'other means'. Average follow-up 28.3 years and employment 19.2 years	Airborne samples; midjet impinger. Silica conversion via bulk samples %	ILO. Most recent radiograph ≥1/0. At least 2 of 3 certified 'B' readers for +ve result	36/936 (4%)	No silicosis analytical methods	Not reported	0.23	NA
		A valid correspondence between Chinese stage I, II, III and ILO 1, 2, 3 exists. ⁴² *Autopsy performed in 131 miners with confirmation of silicosis in 128; 3 false positives. †Cumulative risk (H(t)) = 1 – exp[–sum of (hazards*interval width)]. All studies used job exposure matrices for personal exposure measurements. Study conversion factors were used where necessary. ILO, International Labour Organisation.								

Table 2 Newcastle–Ottawa Scale (NOS) quality assessment tool		
Study	Domains of point loss in NOS scale	Score out of 7
Cohort studies		
Hnizdo and Sluis-Cremer, 1993 ¹⁹	Exposure measure	6
Steenland and Brown, 1995 ¹⁴	–	7
Hughes <i>et al</i> , 1998 ²²	–	7
Chen <i>et al</i> , 2005 ¹⁰	Exposure measure, lack of outcome at onset	5
Liu <i>et al</i> , 2013 ²⁵	Exposure measure, lack of outcome at onset	5
Cross-sectional studies		
Kreiss and Zhen, 1996 ¹⁸	–	7
Rosenman, 1996 ²³	Non-respondents/comparability	6
Miller <i>et al</i> , 1998 ¹¹	–	7
Criteria are described in greater detail in online supplemental file 2 and 4.		

than the previous category. We plotted re-calculated cumulative risks and then compared them with the reported and model fitted cumulative risks. For Chen *et al*,¹⁰ as no coefficients were provided, we used WebPlotDigitizer21 automated extraction of fitted cumulative risk values from figure 2B in the article and extracted every 5 pixels providing 269 paired values.

We performed a dose-response meta-analysis using standard parameters of the dosresmeta package¹⁶ in R (version 4.3.2). The meta-analysis takes log relative risks (including odds ratios (OR) or rate ratios), their confidence intervals (CI) and doses as inputs. Where the number of individuals per category was reported, we calculated the univariate odds of silicosis risk per category, and then the OR for that category compared with the baseline (lowest dose) category. For two studies reporting person-years, incidence rate ratios were calculated using a similar approach.^{22 23} Both OR and rate ratios were converted to log relative risks. CIs were calculated using the delta method. Unless provided, we estimated dose at the midpoint of each category using the methods described above. For Hnizdo and Sluis-Cremer¹⁹ we used data in a second publication,²⁴ as risks were equivalent but more categories were provided. Our descriptive plots showed a differential non-linear response between miners and non-miners. Post-hoc, therefore, we fitted separate restricted cubic spline models for each population. For the miner model (dose groups=55) we chose four knots at default quantiles (0.05, 0.35, 0.65 and 0.95) equivalent to 0.4, 2.0, 3.9 and 12.0 mg/m³-years of RCS exposure. For the non-miner model (dose groups=18) we chose three default knots (0.1, 0.5, 0.9) equivalent to 0.9, 6.2 and 15.4 mg/m³-years. Departure from linearity was tested using the Wald test. To provide context for the current UK and US debate regarding the change of PELs, we fixed the baseline relative risk at 4 mg/m³-years, equivalent to 40 years working at 0.1 mg/m³.

We used ORs as a standardised effect measure assuming limited impact of censoring. This was justified as the loss to follow-up among cohort studies was relatively low (0–9%) and the long silicosis latency and potential cessation of work on diagnosis meant that most or all total exposure occurs prior to disease—for example, in the study by Miller *et al* 5 and 15 participants had >2/1 and >1/1 radiographs on their last interim survey compared with 47 and 105 participants at follow-up.¹¹ Furthermore, the alternative of using ORs for cross-sectional studies and hazard ratios for cohort studies presumes approximate equivalence; when disease prevalence increases significantly across the exposure range this is not the case.

To explore the population-level effect we calculated the absolute risk reduction (ARR). The Steenland study method was used to re-estimate the categorical cumulative silicosis risks for all studies.¹⁴ We then fitted non-parametric locally weighted least squares estimates (LOESS) and extracted the median risk equivalent of 40 years working at 0.1 mg/m³ (4 mg/m³-years). We used this to calculate the ARR when average exposure is reduced to 0.05 mg/m³ (2 mg/m³-years).

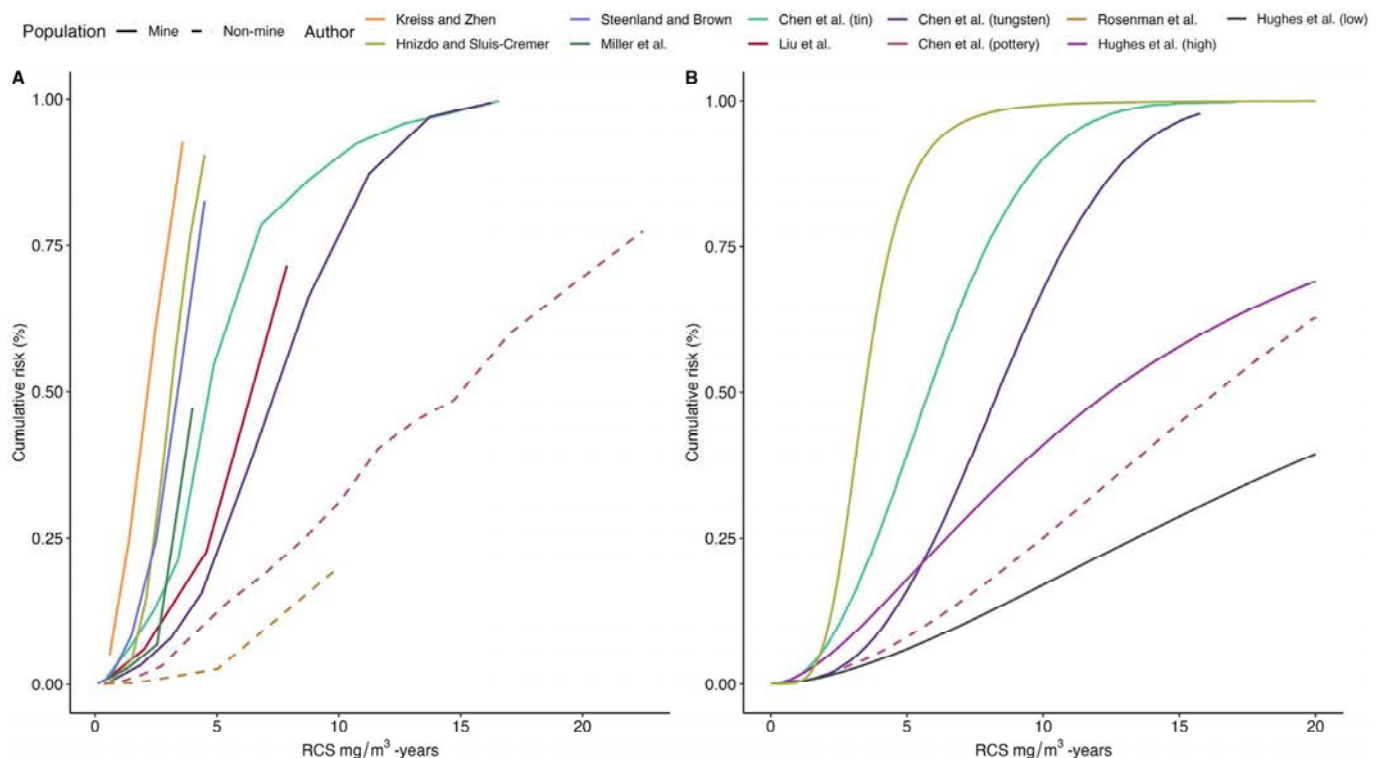


Figure 2 Comparison of cumulative risk of silicosis according to cumulative respirable crystalline silica (RCS) exposure. (A) Life table re-calculated cumulative risk for each study estimated using the Steenland formula. (B) Fitted parametric cumulative risk curve. These were either plotted using the formulae presented in the respective paper or, in the case of Chen *et al.*,¹⁰ as no formulae were provided, plotted using locally estimated least squares regression (LOESS) from a total of 269 paired values across the three cohorts.

Sensitivity analyses

We performed five sensitivity analyses: (1) we included only ILO major category 1 (or equivalent) silicosis; (2) we excluded cross-sectional studies; (3) we included exclusively miner cohorts; (4) we compared high (≥ 0.1 mg/m³) and low intensity studies among miners; and (5) to investigate heterogeneity at lower doses, we included only categories up to 8 mg/m³-years, the limit of model stability. Intensity (analysis 4) was our only pre-specified sensitivity analysis. All codes and data are publicly available (https://github.com/pjhowlett/silica_drma).

RESULTS

Searches in Web of Science, Medline and Embase databases and citation searches yielded 1206 studies (figure 1). After de-duplication, 782 studies underwent title and abstract screening and 50 underwent full-text screening. Of 11 eligible studies, three reported overlapping cohorts and were excluded. Eight studies were therefore included with a total of 65 977 participants of whom 8792 had silicosis. The proportion with silicosis ranged between 4% and 32%. Agreement between reviewers was fair and substantial for title/abstract and full-text review, respectively (Cohen's kappa 0.46 and 0.70).

Characteristics of studies

Among the eight studies, five were cohort and three were cross-sectional studies (table 1). Chen *et al* reported on three cohorts, resulting in a total of 10 cohorts.¹⁰ Of these, six cohorts exclusively worked in the mining industry,^{10 11 14 18 19} two exclusively within industrial plants (pottery factory and foundry)^{13 23} and two consisted of workers from both, one with a predominance of miners (26 670/34 018, 78%)²⁵ and the other with an undefined mix.²² Mean or median follow-up from initial exposure ranged from 24 to 37 years in six studies.^{10 14 18 19 22 23} In two other studies, minimum follow-up from first exposure was estimated at 13 years and 26 years, respectively.^{11 13} Six studies used either ILO major category 1 radiographs or equivalent for diagnosis,^{10 18 19 22 23 25} one used death certificates in addition to ILO major category 1 radiographs¹⁴ and one used ILO major category 2 radiographs.¹¹

Average exposures varied within and across cohorts; all averages were above the current US PEL of 0.05 mg/m³. Steenland and Brown

noted a decreasing intensity of exposure from 0.15 mg/m³ in cohorts hired before 1930 to 0.02 mg/m³ after 1950.¹⁴ Hughes *et al* show a differential dose-response among those exposed to intensities of <0.5 mg/m³ compared with >0.5 mg/m³, although this was confounded by higher exposures among early hires.²² A separate study of the Scottish Colliery cohort¹¹ reported a small proportion of hours worked at intensities >1 mg/m³.²⁶

Risk of bias

Overall, the studies were deemed to have a low risk of bias (table 2 and online supplemental file 4). Most longitudinal studies reported frequent radiographs, particularly during employment; however, for one study only two radiographs were taken¹⁴ and in a second the frequency was unclear.²² In cohort studies, loss to follow-up ranged between 0% and 9%. Confirmation of baseline silicosis absence in two Chinese studies was not possible as mandatory chest radiographs were not introduced until 1963.^{10 25} Additional uncertainty due to conversion factors was reflected in the ascertainment of exposure scoring.^{10 19 25} A plot of log relative risks against cumulative exposures among miners (see online supplemental file 5) may suggest greater relative risks in studies with larger standard errors.

Cumulative risk

Re-estimated cumulative risk of silicosis (using the Steenland method) increased more rapidly and was larger in miner cohorts than in non-miner cohorts (figure 2A). In studies where cumulative exposures approached and exceeded 10 mg/m³-years there appeared to be a gradual flattening of the cumulative risk curve. Parametric fitted cumulative risk curves (figure 2B) show similar patterns. Among the parametric curves, the lowest risk is observed among diatomaceous earth industry workers who had low intensity exposure (<0.5 mg/m³); this cohort included an unknown proportion of miners and processing workers.²⁷ Differences in cumulative risk estimates due to different methodology are clinically important, particularly at lower dose ranges of <10 mg/m³-years (figure 3A,B). Applied to all studies and cumulative dose categories compared with the Steenland method, the SAS LIFETEST method underestimated cumulative risk by a median of -7.2% (IQR -1.6% to -20.5%) while fitted risks underestimated cumulative risk by a median of -4.1% (IQR -0.4% to -8.2%).

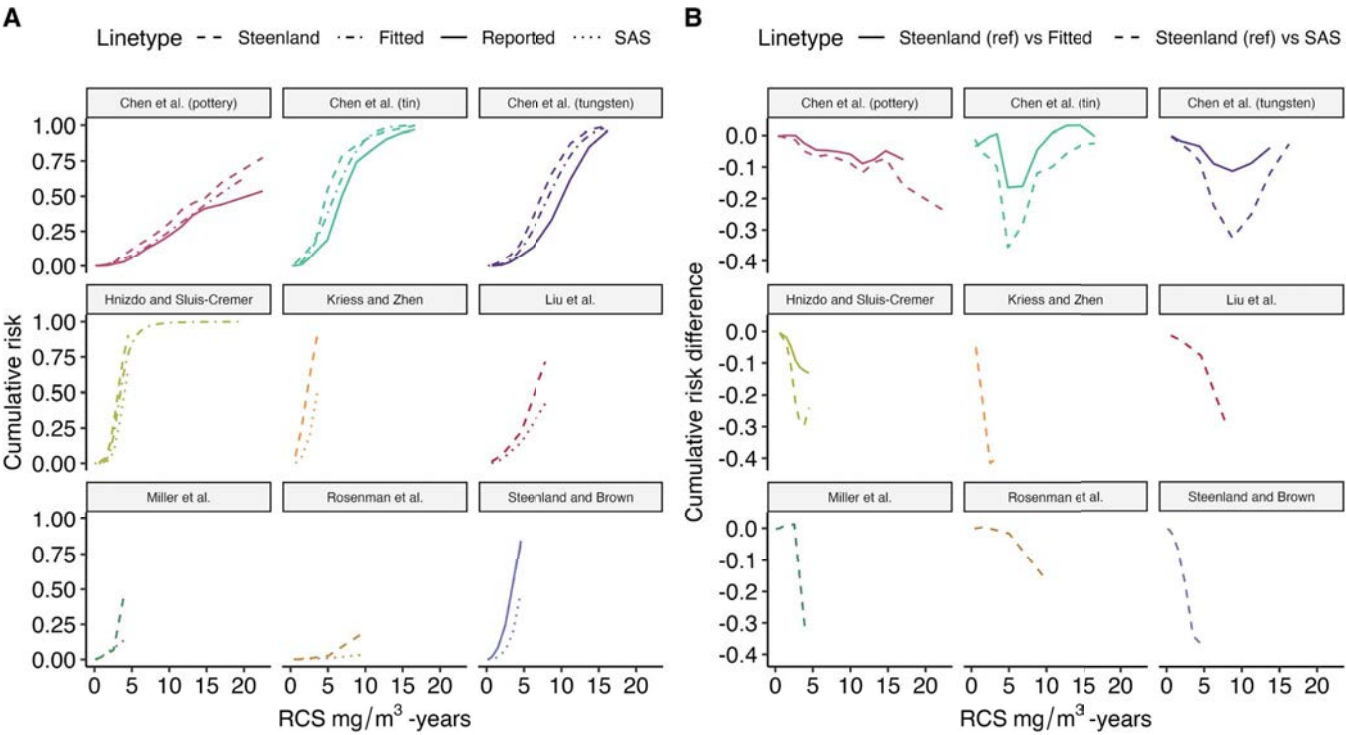


Figure 3 Comparison of calculated, reported and fitted cumulative risk of silicosis among studies providing categorical data (n=8). (A) Comparison of cumulative risks according to cumulative silica exposure for eight cohorts across six studies (NB: Hnizdo and Sluis-Cremer is represented by the full cohort and the selected group of only those who were active miners and attended an annual screening programme). (B) Re-representation of the data as the difference between the SAS LIFETEST formula and other methods according to cumulative silica exposure. This plot uses the same cohorts for A and B. These are represented by the same positioning and colour.

Dose-response meta-analysis

Among miners, the estimated relative risk reduction attributable to a reduction from 4 mg/m³-years silica exposure (equivalent to 40 years work at 0.1 mg/m³ intensity) to 2 mg/m³-years (equivalent to 40 years work at 0.05 mg/m³ intensity) is 0.23 (95% CI 0.18 to 0.29) (table 3). Heterogeneity was very high (I²=92.9%). Among non-miners, a similar reduction from 4 mg/m³-years to 2 mg/m³-years resulted in a relative risk of 0.55 (95% CI 0.36 to 0.83). Heterogeneity was high (I²=77.0%). Both relationships were non-linear (Wald test p<0.001). The dose-response meta-analysis fitted curves show a more rapid increase in relative risk of silicosis among miners than non-miners at cumulative doses of <10 mg/m³-years (figure 4). Compared with the primary analysis, none of the sensitivity analyses retaining the mining/non-mining stratification resulted in meaningful differences to the relative risk (see online supplemental file 6). Models stratified by exposure intensity resulted in larger relative risk estimates for low intensity cohorts. Restricting to exclusively miner cohorts and dose categories <8 mg/m³-years reduced the I² to 74.1%. The reduced heterogeneity at lower doses can be visualised when log relative risks are plotted against cumulative exposures (see online supplemental file 5).

For miners, the median estimated cumulative risk of silicosis from LOESS models at 4 mg/m³-years was 420 per 1000. If cumulative exposure was reduced to 2 mg/m³-years, the ARR was 323 (95% CI 298 to 344) fewer cases per 1000 miners. For non-miners, at 4 mg/m³-years the median estimate was 51 cases per 1000. If cumulative exposure was reduced to 2 mg/m³-years, this resulted in 23 (95% 9 to 33) fewer cases per 1000 non-miners. Data were only available from two non-mining studies, which demonstrate different cumulative risks with silicosis at 4 mg/m³-years (2.0% and 8.2%). Further LOESS cumulative risk estimates are shown in online supplemental file 7.

DISCUSSION

Previous narrative reviews have not rigorously quantified the relationship between cumulative silica exposure and silicosis risk. Our

systematic review found the cumulative silicosis risk was higher among mining cohorts than non-mining cohorts at comparable cumulative silica exposure levels. Among mining cohorts, despite very high heterogeneity (I²=93%), we found a reduction from 4 to 2 mg/m³-years cumulative silica exposure was associated with a 77% (95% CI 71% to 82%) reduction in silicosis risk. This is equivalent to an average silica intensity reduction from 0.1 to 0.05 mg/m³ experienced over a 40-year average working lifetime. A recent systematic review suggests this level of average exposure reduction is achievable.²⁸ Among non-mining studies, the reduction from 4 to 2 mg/m³-years was associated with a 45% (95% CI 34% to 67%) reduction in silicosis risk (I²=77%). These relative risk reductions result in meaningful absolute reductions. Among miners, the reduction from 4 to 2 mg/m³-years resulted in 323 (95% CI 298 to 344) fewer cases per 1000, while for non-miners this figure was 23 (95% CI 9 to 33) fewer cases per 1000.

Previous reviews used reported and fitted cumulative risk values directly from studies to infer disease burden at different exposure levels.^{7 12} Our study suggests these inferences may be imprecise because the cumulative risk methodology and underlying estimatiator assumptions varied across studies, resulting in clinically relevant differences in estimates. These differences are apparent at cumulative exposure values of <5 mg/m³-years, a highly relevant range in our review. Furthermore, a limitation of the LIFETEST method^{10 19 20} is the assumption that all intervals are equal. We used the Steenland method¹⁴ to account for uneven intervals.

Table 3 Comparison of the relative risk and absolute risk reduction of silicosis at a cumulative respirable crystalline silica exposure of 2 mg/m³-years versus 4 mg/m³-years among miners and non-miners

	Risk ratio at reference 4 mg/m ³ -years	Risk ratio at 2 mg/m ³ -years (95% CI)	Absolute risk reduction of 2 vs 4 mg/m ³ -years per 1000 persons (95% CI)
Miners	1	0.23 (0.18 to 0.29)	323 (298 to 344)
Non-miners	1	0.55 (0.36 to 0.83)	23 (9 to 33)

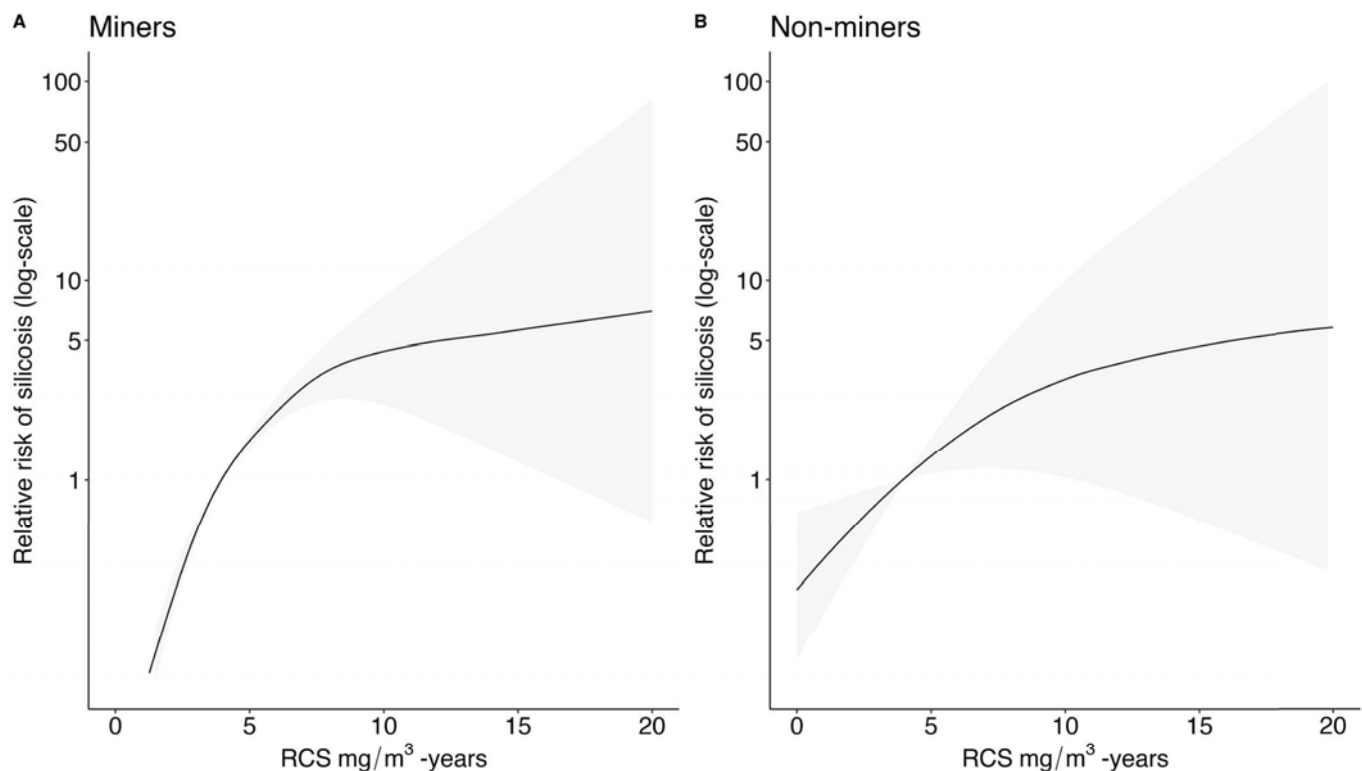


Figure 4 Dose-response meta-analysis of the relative risk of silicosis according to cumulative respirable crystalline silica (RCS) exposure. The reference category with a relative risk of 1 is fixed at 4 mg/m³-years, equivalent to 40 years working at 0.10 mg/m³. As the dose-response method would not allow for all persons in a category to achieve the outcome, 4 of the total 77 categories were combined. (A) Predicted increase in relative risk among mining cohorts (n=8 cohorts, providing 55 individual data points) using a restricted cubic spline model. Four knots at default quantiles were chosen (0.5, 0.35, 0.65 and 0.95), equivalent to 0.4, 2.0, 3.9 and 12.0 mg/m³-years. Heterogeneity was very high ($I^2=92.9\%$). (B) Predicted increase in relative risk among non-mining cohorts (n=2 cohorts, providing 18 individual data points). Three default knots were chosen (0.1, 0.5, 0.9), equivalent to 0.93, 6.2, and 15.4 mg/m³-years. Heterogeneity was high ($I^2=77.0\%$).

One previous meta-analysis used a lifetable approach to calculate rate ratios for silicosis mortality²⁹ and demonstrates a similar shape to our findings with values between those of miners and non-miners (see online supplemental file 8). This may be explained by four of the six studies including non-miners and a relatively fixed non-silicosis mortality quantity across categories. Our ARR values are in keeping with estimates from previous reviews outlined in the introduction.^{7 12}

Our inclusion of two non-mining studies is too few to draw generalisable conclusions and is an oversimplification of the underlying diversity of industries. For example, a dose-response relationship has not been studied in current silicosis outbreaks with very high RCS exposures due to artificial stone² and sand blasting.³⁰ Choosing accelerated disease as an outcome or considering intensity as an exposure may provide early answers to clinically important questions. Other non-miner populations demonstrate a low incidence. For example, few cases were observed among Swedish and Chinese foundry workers^{31 32} and a similar relative risk profile to our study was observed among US industrial sand workers and German porcelain workers.^{33 34} One potential reason for differential responses between miner and some non-miner industries is the proportion of occluded (and thus biologically inactive) surfaces; when adjusted for the cumulative risk discrepancy between pottery and mining largely disappeared.¹⁰ Occlusion has also been demonstrated by aluminosilicates in coal mining.³⁵ Alternative explanations include measurement error—that is, that (non-personal) airborne sampling in open workplaces overestimates true exposure. Importantly, given the range of industries, co-exposures and fatal recent outbreaks, caution is needed in drawing any conclusions until further (industry-specific) data are available.

Supporting previous assertions,^{7 12} we were able to quantify significant heterogeneity in our meta-analysis and dose-response analysis. We observed reduced but persistently high heterogeneity at lower dose ranges and in exclusively miner cohorts. Nevertheless,

if caveated with the understanding that the variance in our estimates is almost exclusively due to between-study heterogeneity rather than statistical variability, we believe our meta-analysed estimates still provide clinically meaningful information. This is particularly true given the effect size, the importance of the policy question regarding chronic low exposures, the lack of alternative better methods and the absence of upcoming study data.

We observed an attenuation of the increase in the relative risk of silicosis among both miner and non-miner analyses at higher ranges of cumulative exposure. A clear discussion of the potential explanations is provided by Stayner et al.³⁶ Of particular relevance are the healthy worker effect described in high exposure miners,¹ the presence of a (yet undiscovered) resistant phenotype, misclassification of the exposure or outcome (for example, silica conversion errors have been suggested),³⁷ saturation of biological disease pathways at higher silica exposures and potential modifying factors. Higher intensity exposure has been considered a potentiator for silicosis,^{22 26} but in our case this was not obviously apparent.

Study limitations

Our study has important limitations. Most ILO cut-offs were 1/1 or 1/0. The absence of symptoms at lower ILO grades may limit the overall clinical impact estimated by the silicosis ARR, although further predicting symptomatic individuals at lower ILO grades is challenging.⁵ Due to unavailability of data we were unable to estimate ARRs at higher ILO thresholds. Importantly, in addition to silicosis, silica exposure has multiple often dose-response detrimental health effects; the silicosis ARR therefore represents the minimum potential health benefit of lowering permissible limits. Confounding and effect modification in the exposure-response relationship is possible: intensity,^{22 26} age,¹⁴ altitude¹⁸ and calendar-time^{14 18 22} have been suggested. However, none are conclusive and our univariate relationship remains a valid model. Substantial methodological differences in RCS measurements exist^{10 37} and

there is a risk of measurement error. While this error may be random, it is potentially more pronounced in historical samples. Our grouping of miner and non-miner cohorts may incur misclassification; two miner cohorts included some non-miners, others potentially include non-mining job roles. The effect is unclear, although restriction to exclusively miner cohorts suggests similar effect sizes with marginal heterogeneity reduction. Despite stringent inclusion criteria requiring raw categorical data and prolonged follow-up, we were able to include most studies in previous reviews.^{7 12} Most studies had longer follow-up than our selection criteria and cohort loss to follow-up was low, limiting the concern of complete ascertainment of silicosis cases. However, selection bias due to loss to follow-up remains likely, particularly in the cross-sectional studies. The inclusion of different diagnostic criteria such as autopsy may introduce a differential bias, although our sensitivity analysis did not suggest this. Future research is needed to adjust for the effect of sub-radiological disease. The suggestion of increased relative risk among studies with large standard errors implies possible publication bias. However, with few studies over many decades and other potential explanations, it is unclear. Four full-text studies were not in English, online translation was not feasible and an important language bias exists. On reflection, our choice of the NOS is unlikely to capture the full extent of bias present in our studies. The results, particularly quantitative, should therefore be interpreted cautiously. While the assumptions required to choose ORs as the preferable unit of relative risk may introduce differential bias, we believe homogenising the unit of relative risk was the preferable option.

CONCLUSION

Despite limitations, our study represents an important advance in answering a centuries-old question that remains globally relevant. Using reproducible and transparent methods, we have demonstrated clinically meaningful results that provide a strong argument for lowering RCS permissible exposure limits, particularly among miners, from 0.1 mg/m³ to 0.05 mg/m³. With supportive measures this change is possible. Further research among non-mining industries and in developing economies is warranted. Modern cohort study techniques mean prolonged follow-up is cheaper and easier and studies that associate carefully collected exposures to the risk of silicosis are feasible.

X Patrick Howlett @tweetpaddy

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Contributors PH: guarantor, writing – original draft preparation, conceptualisation, methodology, project administration, data collection, data curation, visualisation, formal analysis. JG: original draft preparation, methodology, project administration, data collection, data curation, visualisation, formal analysis. ML: formal analysis, writing – review and editing. JF: conceptualisation, project administration, supervision, writing – review and editing.

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O montelucaste é útil no controlo da apneia obstrutiva do sono em crianças com síndrome de Down?

CONTEXTO CLÍNICO

Um menino de 6 anos de idade com síndrome de Down (SD) apresentou-se em clínica pediátrica local com histórico indicativo de apneia obstrutiva do sono (AOS). O exame clínico revela que a criança demonstra respiração bucal e que as suas amígdalas estão aumentadas. Os pais estão interessados em explorar opções não cirúrgicas. Deve ser iniciado o tratamento com montelucaste?

QUESTÃO CLÍNICA ESTRUTURADA

Em crianças em idade escolar com SD (paciente), o montelucaste (intervenção) reduz a gravidade da AOS (resultado)?

ESTRATÉGIA DE PESQUISA

Foi efetuada uma revisão exaustiva da literatura utilizando a PubMed e a Web of Science em agosto de 2022. Foram utilizados os seguintes termos: Título/Abstract: [leukotriene*]OR[montelukast]OR[anti-inflammatory] OR[anti inflammatory] E Title/Abstract:[Trisomy 21]OR[Down syndrome] or[syndrome] AND Title/Abstract:[sleep disordered breathing]OR[sleep related breathing disorder] OR[obstructive sleep apnea/apnoea] Esta pesquisa revelou 93 resultados. Foram revistos os títulos e os resumos. Foram removidos 91 artigos pelas seguintes razões: não relacionados com a questão clínica (n=63), artigos de revisão não sistemática (n=18), opinião de peritos ou linhas orientadoras (n=2), protocolo apenas para uma revisão sistemática (n=1) e exclusão de crianças com SD (n=7). No final, foram incluídos dois estudos, que se encontram resumidos no quadro 1. Uma revisão das bibliografias revelou mais dois estudos potenciais, mas estes foram removidos após a revisão do texto completo devido à falta de relevância para a questão clínica.

COMENTÁRIO

A AOS é mais prevalente, é grave e está associada a piores resultados médicos e neurocognitivos em crianças com SD. A adenotonsilectomia é o tratamento primário. Contudo, não é um procedimento universalmente curativo e a falta de um acesso atempado à cirurgia constitui um obstáculo ao tratamento. Dadas estas limitações, está em curso uma investigação sobre a eficácia de opções terapêuticas alternativas. Foram publicadas várias revisões sistemáticas de elevada qualidade sobre o tema do montelucaste e da AOS.^{1,2} A literatura sobre crianças sem SD sugere que o montelucaste é o tratamento mais eficaz para a redução da gravidade e dos sintomas da AOS.¹⁻⁴ No entanto, os artigos incluídos nas revisões não se centram (e excluem frequentemente) as crianças com SD, pelo que os resultados não podem ser aplicados a esta questão clínica.

A exclusão de crianças com condições médicas subjacentes da maioria dos estudos nas fases iniciais desta revisão revela um viés mais amplo no contexto da investigação, reduzindo a aplicabilidade dos estudos ao tratamento em mundo real de crianças com deficiência.

Os dois estudos de Yu et al⁵ e Howard et al⁶ apresentam uma relação direta com esta questão clínica. No entanto, tratam-se de revisões retrospectivas, o que significa que as evidências são de um nível inferior. Em ambos os estudos, o montelucaste não conduziu a uma melhoria do Índice de Apneia e Hipopneia (IAH). Os autores concluíram que os seus resultados não apoiavam a utilização de montelucaste nesta coorte. A amostra do estudo foi reduzida e as taxas de atrito podem ter afetado os resultados. A ausência de maiores evidências nesta coorte é problemática e afeta a qualidade dos resultados. As razões para a ausência de melhores resultados clínicos e estatisticamente significativos na AOS com montelucaste em crianças com SD podem estar relacionadas com o tamanho e o desenho do estudo. No entanto, existem diferenças fisiológicas entre crianças com SD e sem SD que também podem afetar a forma e o momento em que o montelucaste é eficaz no tratamento dos sintomas da AOS. A fisiopatologia da asma em crianças com SD é diferente e parece não ser causada ou estar relacionada com tendências atópicas. A rinite alérgica também se revela menos comum em crianças com SD. As razões para este facto podem incluir a disfunção ou desregulação das células T, a interferência na produção de citocinas essenciais no cromossoma 21 e a expressão reduzida de determinados leucotrienos, que podem alterar a função dos leucotrienos e a resposta ao montelucaste.⁷⁻¹⁰ A farmacologia específica do montelucaste em crianças com SD continua a ser uma área de estudo em curso. Justifica-se a realização de ensaios controlados e aleatorizados robustos sobre a utilização do montelucaste em crianças com SD.

Yu et al⁵ referiram a utilização de montelucaste como tratamento suplementar em crianças com SD. Verificaram que 59% dos doentes apresentava um histórico de adenoidectomia ou amigdalectomia há mais de 2 anos antes da inclusão no estudo, 62% dos doentes receberam montelucaste e corticosteroides inaláveis em combinação e apenas 31% dos doentes receberam montelucaste como tratamento primário para a AOS no âmbito do estudo. O estudo de Howard et al⁶ excluiu os doentes com duplo tratamento médico na altura da revisão ou com tratamento cirúrgico em qualquer altura antes da revisão. As diferenças nos critérios de inclusão destes estudos e a utilização do montelucaste como terapêutica primária ou suplementar são importantes de salientar, embora os resultados não demonstrem qualquer melhoria nos sintomas da AOS em nenhum dos estudos.

As questões relacionadas com o perfil de segurança do montelucaste estão bem documentadas. Foram reportados distúrbios do sono, agitação e distúrbios comportamentais, 11 mas a prevalência de efeitos adversos varia muito na literatura (0%-31,9%)^{3,4,11}. Embora a grande variedade de efeitos adversos reportados possa ser atribuída ao desenho do estudo e ao seguimento, a indicação, a dose e a duração do tratamento, além da utilização de montelucaste como tratamento suplementar ou primário, também podem ser relevantes. As revisões sistemáticas da utilização do montelucaste na AOS possuem pouca informação sobre o seu perfil de segurança, embora tenham sido reportadas náuseas e cefaleias.¹² O perfil de segurança de montelucaste em crianças com SD não foi referido por nenhum dos dois estudos incluídos, nem existe qualquer literatura publi-

Table 1 Summary of studies					
Citation	Study group	Study type	Outcome	Key result	Comments
Yu et al ⁵ ; <i>Journal of Clinical Sleep Medicine</i> 2020; 16(6)	Children with DS with mild OSA aged 1–17 years; montelukast or intranasal steroids vs watchful waiting 89 children; 50 receiving montelukast.	Retrospective cohort study (level 4).	Resolution of OSA as defined by obstructive AHI<1.	No resolution of OSA in the medication or observation groups. Median obstructive AHI in the medication group was 2.8 (IQR 2.2–3.6) at baseline and 3.5 (IQR 1.4–4.8) at follow-up.	There is insufficient evidence to support the use of montelukast to treat OSA in children.
Howard et al ⁶ ; <i>The Laryngoscope</i> 2020; 130(7)	Children with DS with mild OSA aged 0–17 years; montelukast or intranasal steroids versus oxygen therapy versus watchful waiting 24 children; 8 receiving montelukast.	Retrospective cohort study (level 4).	Obstructive AHI<1 on follow-up.	No significant change in AHI in any treatment group.	These findings do not support the use of montelukast to treat mild OSA in children with DS
AHI, Apnoea Hypopnoea Index; DS, Down syndrome; IQR, Interquartile Range; OSA, obstructive sleep apnoea.					

cada sobre o tópico dos efeitos adversos de montelukaste em crianças com SD e AOS. No entanto, tendo em conta os efeitos adversos conhecidos de montelukaste na população em geral, é necessário ser prudente na consideração de iniciar o tratamento com montelukaste.

Atualmente, montelukaste não é um tratamento baseado em evidências para AOS em crianças com SD. Dadas as diferenças fisiológicas na função imunitária e na expressão de leucotrienos em crianças com SD, o peso dos potenciais efeitos adversos e a ausência de evidências sobre a eficácia do tratamento, montelukaste não deve ser prescrito para tratamento da AOS em crianças com SD.

Clinical bottom line

- ⇒ Children with Down syndrome (DS) and obstructive sleep apnoea (OSA) should be managed with adenotonsillectomy or non-invasive ventilation (moderate, grade B).
- ⇒ There is no evidence to support the use of montelukast in the treatment of OSA in children with DS (low, grade C).

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