

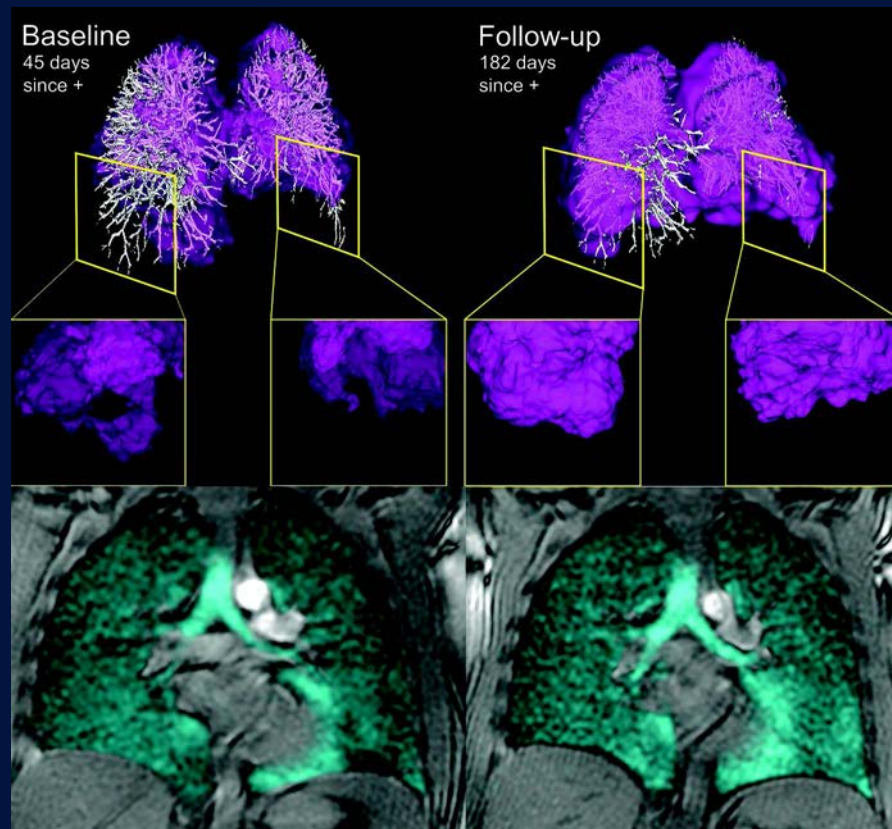
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa



thorax.bmj.com

adc.bmj.com



British
Thoracic
Society

RCPCH
Royal College of
Paediatrics and Child Health
Leading the way in Children's Health

BMJ

CURSO DE ESPECIALIZAÇÃO DOENÇAS RESPIRATÓRIAS E DO SONO DA CRIANÇA



CURSOS AVANÇADOS EM REGIME B-LEARNING

CURSO	CURSOS AVANÇADOS	COORDENADORES	METODOLOGIA		DATAS	FTC'S
			B-LEARNING	PRESENCIAL		
1	FUNÇÃO RESPIRATÓRIA E FISIOLÓGIA DO EXERCÍCIO NA CRIANÇA	TERESA BANDEIRA, ANA MARGARIDA SILVA, CAROLINA CONSTANT	1,3	7, 14	11, 12 NOV 2022 25, 26 NOV 2022	18
2	ENDOSCOPIA E IMAGIOLOGIA DO APARELHO RESPIRATÓRIO NA CRIANÇA	ANA SAIANDA, CAROLINA CONSTANT, LIA OLIVEIRA	1, 2, 3, 4	5, 6	11, 18, 19 NOV 2022 24, 25 FEV 2023 17, 18 MAR 2023	22
3	TECNOLOGIAS RESPIRATÓRIAS, FARMACOLOGIA E REABILITAÇÃO NA CRIANÇA COM DOENÇA RESPIRATÓRIA CRÓNICA COMPLEXA	TERESA BANDEIRA, LUÍSA PEREIRA, ROSÁRIO FERREIRA, ANA SAIANDA, CAROLINA CONSTANT, LIA OLIVEIRA, RICARDO FERNANDES	1, 3, 4, 9, 17	8	11, 12 NOV 2022 24 FEV 2023 28, 29 ABR 2023 5, 6 MAI 2023	17,5
4	DOENÇAS RESPIRATÓRIAS E OUTRAS PERTURBAÇÕES DO SONO	ROSÁRIO FERREIRA, LIA OLIVEIRA	10, 11, 13	8, 12	18, 31, MAR 2023 1, 14, 15 ABR 2023 5, 6 MAI 2023	16

Módulos:

- 1- Anatomia e Fisiologia do Aparelho Respiratório
- 2- Doenças respiratórias agudas. Urgências e Emergências Respiratórias
- 3- Doença Pulmonar Crónica e Malformações Congénitas
- 4- Imagiologia torácica
- 5- Exames laboratoriais, microbiológicos e alergológicos
- 6- Endoscopia Brônquica
- 7- Função Pulmonar; 8- Tecnologias Respiratórias
- 9- Terapêutica Farmacológica das doenças respiratórias
- 10- Bases Fisiológicas do Sono

- 11- Doenças respiratórias e outras perturbações do sono
- 12- Diagnóstico em doenças do sono
- 13- Terapêutica Farmacológica das doenças do sono
- 14- Fisiologia Clínica da Respiração e do exercício. Prescrição de exercício e reabilitação
- 15- Influências e trajetórias em saúde respiratória: ambientes, nutrição, opções terapêuticas e transição
- 16- Bioestatística e Meta-análise
- 17- Educação e Comunicação em Ciências da Saúde

ORGANIZAÇÃO E FUNCIONAMENTO



CONSULTE AQUI



Journal of the British Thoracic Society
Impact Factor: 9.203

Editors-in-Chief

N Hart (UK)
G Jenkins (UK)
AR Smyth (UK)

Deputy Editor

R Chambers (UK)
C Wainwright (Australia)

Associate Editors

D Baldwin (UK)
S Bloom (UK)
HJ Bogaard (The Netherlands)
S Christenson (USA)
T Coleman (UK)
A Condliffe (UK)
GJ Criner (USA)
L Donnelly (UK)
A Floto (UK)
M Griffiths (UK)
R Hallifax (UK)
L Heaney (UK)
N Hopkinson (UK)
S Janes (UK)
DL Jarvis (UK)
G Kaltsakas (UK)

B Kampman (UK)
W Lenney (UK)
O M Kon (UK)
B Mokhesi (USA)
I Noth (USA)
J-L Pepin (France)
M Polkey (UK)
J Quint (UK)
K Robinson (USA)
B Sage (UK)
S Saglani (UK)
C Scotton (UK)
R Stevens (USA)
P Wark (Australia)
T Wilkinson (UK)
P Wolters (USA)

Guidelines Associate Editor

I Du Rand (UK)

Statistical Editors

N Beckley-Hoelscher (UK)
A Douiri (UK)
C Flach (UK)
C Jackson (UK)
S Nevitt (UK)
L Stanberry (USA)
S Stanojevic (USA)
I Stewart (UK)
R Szczesniak (USA)
B Wagner (USA)
Y Wang (UK)

Journal Club Editor

P Murphy (UK)

Multimedia Editor

R Moses (UK)

President, British Thoracic Society

Rachael Moses

Editorial Office

Thorax, BMJ Journals, BMA House,
Tavistock Square, London, WC1H 9JR, UK
T: +44 (0)20 7383 6373

E: thorax@bmj.com

Twitter: @ThoraxBMJ

ISSN: 0040-6376 (print)

ISSN: 1468-3296 (online)

Disclaimer: Thorax is owned and published by the British Thoracic Society and BMJ Publishing Group Ltd, a wholly owned subsidiary of the British Medical Association. The owners grant editorial freedom to the Editor of Thorax.

Thorax follows guidelines on editorial independence produced by the World Association of Medical Editors and the code on good publication practice of the Committee on Publication Ethics.

Thorax is intended for medical professionals and is provided without warranty, express or implied. Statements in the Journal are the responsibility of their authors and advertisers and not authors' institutions, the BMJ Publishing Group Ltd, the British Thoracic Society or the BMA unless otherwise specified or determined by law.

Acceptance of advertising does not imply endorsement. To the fullest extent permitted by law, the BMJ Publishing Group Ltd shall not be liable for any loss, injury or damage resulting from the use of Thorax or any information in it whether based on contract, tort or otherwise. Readers are advised to verify any information they choose to rely on.

Copyright: © 2023 BMJ Publishing Group Ltd and the British Thoracic Society. All rights reserved; no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior permission of Thorax. Thorax is published by BMJ Publishing Group Ltd, typeset by Exeter Premedia Services Private Ltd, Chennai, India and printed in the UK on acid-free paper. Thorax (ISSN No: 0040-6376) is published monthly by BMJ Publishing Group and distributed in the USA by Air Business Ltd. Periodicals postage paid at Jamaica NY 11431.

POSTMASTER: send address changes to Thorax, Air Business Ltd, c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA

Índice Volume 7 Número 2 Thorax com artigos do Archives of Disease in Childhood março / abril 2023

Edição Portuguesa N.º 2 março / abril 2023 - Volume 7

57 Editorial

59 Artigo original

59 Desvendar o papel da utilização de máscara de proteção respiratória no controlo do SARS-CoV-2 nas escolas: um estudo quase experimental enquadrado numa coorte populacional na Catalunha (Espanha)

64 Influência das epidemias e das pandemias na utilização dos SU pediátricos: uma revisão sistemática

70 Epidemiologia respiratória

70 Desfechos respiratórios e alérgicos entre crianças de 5 anos expostas a pesticidas

79 Asma

79 Efeito a longo prazo da asma no desenvolvimento da obesidade entre os adultos: um estudo de coorte internacional, ECRHS

85 Doença pulmonar obstrutiva crónica

85 Proibição de fumar em espaços fechados a nível nacional e impacto sobre os comportamentos tabágicos e a função pulmonar: uma experiência natural em duas populações

91 Tuberculose

91 Obstrução do fluxo de ar e disfunção das pequenas vias respiratórias na sequência de uma tuberculose pulmonar: um inquérito transversal

97 Fibrose quística

97 Além fronteiras: sobrevivência à fibrose quística entre Austrália, Canadá, França e Nova Zelândia



Thorax

com artigos do
**Archives of
Disease in Childhood**

Edição bimestral em língua portuguesa

Editada por:

Medjournal

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

General Manager
António Gonçalves

Diretores Médicos
Carlos Robalo Cordeiro
Jaime Correia de Sousa
Mário Morais de Almeida
Teresa Bandeira

A Medjournal não se responsabiliza pela opinião expressa dos autores.
Proibida a reprodução total ou parcial sob qualquer forma, sem autorização prévia do BMJ Publishing Group.



Editor in Chief

Nick Brown

Senior Editor

Rachel Agbeko

Deputy Editors

Claire Lerner (Commissioning)
Ben Stenson (Fetal & Neonatal)
Ian Wacogne (Education & Practice)

Editorial Office

Heather Burris

Advocacy Editor

Archives of Disease in Childhood
BMJ Publishing Group Ltd

BMA House

Tavistock Square

London WC1H 9JR, UK

E: info.adc@bmj.com

Twitter: @ADC_BMJ

Senior Production Editor

Malcolm Smith

E: production.adc@bmj.com

ISSN: 0003-9888 (print)

ISSN: 1468-2044 (online)

Impact factor: 4.918

Journal of the Royal College of

Paediatrics and Child Health

Disclaimer: ADC is published by BMJ

Publishing Group Ltd (a wholly owned subsidiary of the British Medical Association) and the Royal College of Paediatrics and Child Health. The owners grant editorial freedom to the Editor of ADC. ADC follows guidelines on editorial independence produced by the World Association of Medical Editors and the code on good publication practice of the Committee on Publication Ethics.

ADC is intended for medical professionals and is provided without warranty, express or implied. Statements in the journal are the responsibility of their authors and advertisers and not authors' institutions, the BMJ Publishing Group Ltd, the Royal College of Paediatrics and Child Health or the BMA unless otherwise specified or determined by law. Acceptance of advertising does not imply endorsement.

To the fullest extent permitted by law, the BMJ Publishing Group Ltd shall not be liable for any loss, injury or damage resulting from the use of ADC or any information in it whether based on contract, tort, or otherwise. Readers are advised to verify any information they choose to rely on.

Copyright © 2023 BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health.

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without prior permission.

ADC is published by BMJ Publishing Group Ltd, typeset by Nova Techset Private Limited, Bengaluru & Chennai, India and printed in the UK on acid-free paper from sustainable forests. ADC (ISSN No: 0003-9888) is published monthly by BMJ Publishing Group Ltd and is distributed in the USA by Air Business Ltd. Periodicals postage paid at Jamaica NY 11431 and additional mailing offices. POSTMASTER: send address changes to Archives of Disease in Childhood, Air Business Ltd, c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA

Thorax

ORIGINALITY, RIGOUR AND EXCELLENCE
IN RESPIRATORY MEDICINE

Impact Factor: 9.203

Journal of the
British Thoracic Society

Editorial Board

H Aranibar (Chile)
R Beasley (New Zealand)
J Brown (UK)
J Celedon (USA)
T Fardon (UK)
P Gibson (Australia)
J Grigg (UK)
ML Han (USA)
F Holguin (USA)
I Janahi (Qatar)
A Jones (UK)
A Knox (UK)
F Maltais (Canada)
D Mannino (USA)
S Nathan (USA)
I Pavord (UK)
F Ratjen (Canada)
J Scullion (UK)
J Simpson (UK)
M Steiner (UK)
A Torres (Spain)
Z Udwadia (India)
D Warburton (USA)
M Whyte (UK)

President, British Thoracic Society

Rachael Moses

Publisher

Claire Rawlinson

Associate Publisher

Henry Spilberg

Guidelines for Authors and Reviewers

Full instructions are available online at <http://thorax.bmj.com/pages/authors/>. Articles must be submitted electronically <https://mc.manuscriptcentral.com/thorax>. Authors retain copyright but are required to grant *Thorax* an exclusive licence to publish <https://thorax.bmj.com/pages/authors/>

Aims and Scope: *Thorax* aims to cover all areas of respiratory medicine from paediatric to adults through publishing original papers, systematic reviews and meta-analyses, trial protocols, state of the art reviews, invited editorials, case-based discussions and images. The priorities are originality, rigour and excellence.

Editors-in-Chief

M Griffiths (UK)
C O'Kane (UK)
J Quint (UK)

Deputy Editors

A Bottle (UK)
R Chambers (UK)
M Shankar-Hari (UK)
C Wainwright (Australia)

Associate Editors

M Bafadel (UK)
D Baldwin (UK)
B Blackwood (UK)
K Blythe (UK)
HJ Bogaard (The Netherlands)
F Brimms (Australia)
B Connolly (UK)
GJ Criner (USA)
C Dean (UK)
D Dockrell (UK)
A Floto (UK)
J Honda (USA)
N Hopkinson (UK)
D Jackson (UK)
C Janson (Sweden)
G Kaltsakas (UK)
D Kiely (UK)
B Kirenga (Uganda)
M Knauer (UK)
O M Kon (UK)
G Lee (Australia)
W Lenney (UK)
M Loebinger (UK)
I Mudway (UK)
M Nikolic (UK)
J Park (UK)
J-L Pepin (France)

M Polkey (UK)

J Porter (UK)
R Riha (UK)
L Rose (UK)
J Rylance (UK)
S Saglani (UK)
E Sapey (UK)
R Sauler (USA)
C Scotton (UK)
A Shah (UK)
S Singh (India)
R Stevens (USA)
M Toshner (UK)
K Verhamme (Netherlands)
P Wark (Australia)

Guidelines Associate Editor

I Du Rand (UK)

Statistical Editors

A Douiri (UK)
E Gecili (USA)
M Taghavi Azar Sharabiani (USA)
S Stanojevic (USA)
I Stewart (UK)
R Szczesniak (USA)
Y Wang (UK)

Journal Club Editor

P Murphy (UK)

Social Media Editors

K Diomedes (UK)
P Mehta (UK)

Education Editors

J Park (UK)
S Chatterjee (USA)

Multimedia Editor

Nick Hopkinson (UK)

Contact Details

Editorial Office

Thorax, BMJ Journals, BMA House, Tavistock Square, London, WC1H 9JR, UK

E: thorax@bmj.com

Twitter: @ThoraxBMJ

British Thoracic Society

17 Doughty Street, London WC1N 2PL, UK

T: +44 (0)20 7831 8778

E: bts@brit-thoracic.org.uk

W: <https://www.brit-thoracic.org.uk/>

Customer Support

For general queries and support with subscriptions:

T: +44 (0)20 7111 1105

E: support@bmj.com

W: <https://myaccount.bmj.com/myaccount/customerservice/support-home.html>

Self-archiving and permissions

E: bmj.permissions@bmj.com

W: bmj.com/company/products-services/rights-and-licensing/

Advertising

W: bmj.com/company/for-advertisers-and-sponsor/

Display Advertising ROW

Sophie Fitzsimmons

T: +44 (0)20 3655 5612

E: sfittsimmons@bmj.com

Online Advertising ROW

Marc Clifford

T: +44 (0)20 3655 5610

E: mclifford@bmj.com

Display & Online Advertising Sales Americas

American Medical Communications (AMC)

T: +1 973 214 4374

E: rgordon@americanmedicalcomm.com

Author Reprints

BMJ Reprints Team

E: admin.reprints@bmj.com

Commercial Reprints ROW

Nadia Gurney-Randall

M: +44 (0)7866 262344

E: ngurneyrandall@bmj.com

Commercial Reprints Americas

Ray Thibodeau

T: +1 267 895 1758

M: +1 215 933 8484

E: ray.thibodeau@contentednet.com

Production Editor

Tasnia Nizam

E: production.thorax@bmj.com

For all other journal contacts:

<https://thorax.bmj.com/pages/contact-us/>

Subscription Information

Thorax is published monthly (subscribers receive all supplements)

Institutional Rates 2023

Print
£1019

Online

Site licences are priced on FTE basis and allow access by the whole institution. Details available online at <http://www.bmj.com/company/bmj-for-institutions/> or contact Subscription (see above right).

Personal Rates 2023

Print (includes online access at no additional cost)
£422

Online only

£227
ISSN 0040-6376 (print)
ISSN 1468-3296 (online)

Personal print or online only and institutional print subscriptions may be purchased online at <http://thorax.bmj.com/pages/subscribe/> (payment by (MasterCard/Visa only).

Residents of some EC countries must pay VAT; for details call us or visit <http://www.bmj.com/company/eu-vat-rates/>

Editorial

Com perto de 800 milhões de casos registados e cerca de 7 milhões de mortes relacionadas, a Organização Mundial de Saúde (OMS) anunciou o final da pandemia COVID-19, aproveitando para salientar que muitos erros foram cometidos, incluindo falta de coordenação, equidade e solidariedade, o que fez com que recursos existentes não fossem adequadamente utilizados para combater o vírus.

Mas indiscutivelmente os profissionais de saúde, no nosso país, tal como a nível global, souberam estar à altura deste tremendo desafio, onde imperava a incerteza e a dúvida, onde a morbilidade e a mortalidade eram à partida desconhecidas.

E muitos foram os profissionais de saúde que, infelizmente, adoeceram e perderam a sua vida, ao serem infetados pelo SARS-CoV-2. A OMS estima que até 180.000 profissionais de saúde possam ter morrido de COVID-19 apenas até maio de 2021, o que para além de trágico, criou uma lacuna considerável na prestação de cuidados de saúde às populações.

E se pode ser considerado positivo o fato de que a taxa de infeções entre profissionais de saúde ter diminuído ao longo do tempo, muito mais atenção deve ser considerada para minimizar este risco no nosso local de trabalho. Aprendemos com lições de que não nos podemos esquecer. Não devemos ser discriminados ou desvalorizados por decisões políticas sem suporte técnico-científico. Temos a obrigação de deixar vivo este legado para quem nos vai suceder no exercício da nossa profissão.

Neste número da revista podem encontrar novamente interessantes artigos, alguns relacionados com a recente pandemia, desde a avaliação da eficácia da utilização obrigatória de máscaras de proteção respiratória nas escolas da Catalunha, à avaliação do impacto das epidemias e pandemias na utilização dos serviços de urgência pediátrica visando influenciar as políticas de saúde, podendo ter de se admitir que ainda são baseadas numa incerteza considerável que deverá ser esclarecida com mais investigação e colaboração internacional.

Ainda na idade pediátrica, salientamos o artigo de Islam et al, “Desfechos respiratórios e alérgicos entre crianças de 5 anos expostas a pesticidas”, onde se comprova os potenciais efeitos nefastos de poluentes de ampla utilização. Sobre a temática da asma, destacamos um artigo de Moitra et al, com resultados do European Community Respiratory Health Survey (ECRHS), um bem conhecido estudo epidemiológico em que o nosso país esteve envolvido, que permitiu concluir que os adultos asmáticos têm um risco mais elevado de desenvolver obesidade do que os não asmáticos, em especial os não atópicos, os que sofrem da doença há mais tempo ou que tomam corticosteroides orais para controlo dos seus sintomas.

O efeito positivo das medidas restritivas ao consumo de tabaco nos espaços interiores, as sequelas clínicas e funcionais após infeção tuberculosa, e os fatores que podem interferir com a esperança média de vida dos doentes com fibrose quística, merecem igualmente a nossa atenção e o renovar do voto de boas leituras,

Mário Morais de Almeida

Editor in Chief

Nick Brown

Senior Editor

Rachel Agbeko

Deputy Editors

Claire Lemer (Commissioning Editor)

Ben Stenson (Fetal & Neonatal)

Neelam Gupta (Education & Practice)

Drug Therapy Editor

Dan Hawcutt

Global Child Health Editor

Trevor Duke

Advocacy Editor

Heather Burris

Paediatric Emergency Medicine Editor

Cynthia Mollen

Health Policy Editor

John Puntis

Images Editor

Mark Tighe

Quality Improvement Editor

Claire Lemer

Adolescent Health Editor

Dougal Hargreaves

Social Media and Archimedes Editor

Bob Phillips

Archivist and Lucina Editor

Colin Powell

Voices Editor

Robert Scott-Jupp

Associate Editors

Karel Allegaert

Diana Baralle

Martin Bellman

Sophie Bennett

Frances Bu'lock

Ronny Cheung

David Cottrell

Louise Fleming

Hadeel Hassan

Peter Hoyer

Fyezah Jehan

Vic Larcher

Anne Kelly

Uzma Khan

Daniel Lumsden

Catherine Peters

Colin Powell

Philippa Prentice

A V Ramanan

Andrew Riordan

Helen Sammons

Natasha Saunders

Robert Tasker

Indi Trehan

Paul Turner

Sunitha Vimalasvaran

Guidelines for Authors and Reviewers

Full instructions are available online at <https://adc.bmj.com/pages/authors/>. Articles must be submitted electronically <https://mc.manuscriptcentral.com/adc>. Authors retain copyright but are required to grant *ADC* an exclusive licence to publish (<https://adc.bmj.com/pages/authors/>)

Archives of Disease in Childhood focuses on all aspects of child health and disease from the perinatal period through adolescence

Statistical Editor

Tim Cole

Statistical Advisors

Emmanouil Bagkeris

Mario Cortina Borja

Sarah Donegan

Sara Godward

Marlous Hall

Katie Harron

Eirini Koutoumanou

Sarah Nevitt

Snehal Pinto Pereira

Deborah Ridout

Andrea Sherriff

Lesley Smith

Angie Wade

International Advisors

Zulfi A Bhutta

Leyla Namazova-Baranova

Education & Practice Section Editors

Best practice

Amanda Gwee

Problem solving in clinical practice

Mark Anderson, Mark Tighe

Interpretations

Sam Behjati, Thomas Waterfield

Epilogue

Mark Tighe, Lisa Brown

Guidelines

Philippa Prentice, Emma Dyer

Picket

Giordano Perez-Gaxiola,

Rebecca Dalrymple, Amanda Friend

Equipped and Equipment

Alice Roueche, Jane Runnacles

Public Health

Ronny Cheung, Rakhee Shah

Research in Practice

Bob Phillips, John Apps

Medicines update

Amanda Gwee



The Journal of the Royal College of Paediatrics and Child Health



ADC is the official journal of NPPG. NPPG members receive online access to *ADC* via the NPPG website.



Don't wait to read the latest *ADC* articles

Most articles accepted for publication in *ADC* are published online well before they appear in a print issue

- Read the latest articles by following the Online First link at the top right of the homepage (adc.bmj.com)
- Sign up for an email alert to be notified when new content is added (adc.bmj.com/cgi/alerts/etoc)
- Comment on the articles in the *ADC* Blog (<http://blogs.bmj.com/adc/>)

Subscription information

Archives of Disease in Childhood is published monthly plus *Fetal & Neonatal* Edition bimonthly and *Education & Practice* Edition bimonthly (subscribers receive all editions and supplements)

Institutional rates 2023

Print
£1210

Online

Site licences are priced on FTE basis and allow access by the whole institution. Print is available for online subscribers; details available online at <http://group.bmj.com/subscribe/?adc> or contact the Subscription Manager in the UK (see above right)

Residents of some EC countries must pay VAT; for details, call us or visit support@bmj.com

Personal rates 2023

Print (includes online access at no additional cost)
£543

Online only
£240

ISSN 0003-9888 (print); 1468-2044 (online)

Personal print or online only and institutional print subscriptions may be purchased online at <https://adc.bmj.com/pages/subscribe/> (payment by Visa/Mastercard only)

Contact Details

Editorial Office

Archives of Disease in Childhood
BMJ Publishing Group Ltd
BMA House, Tavistock Square
London, WC1H 9JR, UK
E: info.adc@bmj.com

Customer Support

For general queries and support with existing and new subscriptions:

T: +44 (0)20 7111 1105

<https://myaccount.bmj.com/myaccount/customerservice/support-home.html>

Self-archiving and Permissions

W: bmj.com/company/products-services/permissions-and-licensing/
E: bmj.permissions@bmj.com

Publisher

Christiane Notarmarco

Associate Publisher

Richard Sands

Publishing Executive

Joshua McAlpine

E: jmc Alpine@bmj.com

Senior Production Editor

Malcolm Smith

E: production.adc@bmj.com

Supplement enquiries

E: rsands@bmj.com

Subscriptions (except USA)

For all subscription enquiries and orders

T: +44 (0)20 7111 1105

<https://adc.bmj.com/pages/subscribe/>

Display Advertising Sales – Rest of World

Sophie Fitzsimmons

T: +44 (0)20 3655 5612

E: sfzsimmons@bmj.com

<https://www.bmj.com/company/for-advertisers-and-sponsor/>

Online Advertising Sales

Marc Clifford

T: +44 (0)20 3655 5610

E: mclifford@bmj.com

<http://group.bmj.com/advertising/>

Display & Online Advertising Sales – North America

American Medical Communications (AMC)

T: +1 973 214 4374

E: rgordon@americanmedicalcomm.com

Author Reprints

BMJ Reprints Team

E: admin.reprints@bmj.com

Commercial Reprints – Rest of World

Nadia Gurney-Randall

T: +44 (0)20 8445 5825

M: 07866 262344

E: ngurneyrandall@bmj.com

Commercial Reprints – North America

Ray Thibodeau

T: +1 267 895 1758 (toll free in the USA)

T: +1 215 933 8484 (outside the USA)

E: ray.thibodeau@contentednet.com

Royal College of Paediatrics and Child Health

5–11 Theobalds Road

London WC1X 8SH

T: +44 (0)20 7092 6000

E: enquiries@rcpch.ac.uk

www.rcpch.ac.uk

For all other *Archives* journal contacts

<http://adc.bmj.com/site/help/index.xhtml>

ARTIGO ORIGINAL

Desvendar o papel da utilização de máscara de proteção respiratória no controlo do SARS-CoV-2 nas escolas: um estudo quase experimental enquadrado numa coorte populacional na Catalunha (Espanha)

Ermengol Coma,¹ Martí Català,² Leonardo Méndez-Boo,¹ Sergio Alonso,³ Eduardo Hermosilla,^{1,4} Enric Alvarez-Lacalle,³ David Pino,³ Manuel Medina,¹ Laia Asso,⁵ Anna Gatell,⁶ Quique Bassat,^{7,8,9,10,11} Ariadna Mas,¹² Antoni Soriano-Arandes,^{13,14} Francesc Fina Avilés,¹ Clara Prats³

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2022-324172>).

For numbered affiliations see end of article.

Correspondence to

Dr Antoni Soriano-Arandes, Paediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; tsorianoarandes@gmail.com

Received 22 March 2022

Accepted 5 August 2022

Published Online First

23 August 2022



► <http://dx.doi.org/10.1136/archdischild-2022-324809>



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Coma E, Català M, Méndez-Boo L, et al. *Arch Dis Child* 2022;108:131–136. doi:10.1136/archdischild-2022-324172

RESUMO

Objetivo Avaliar a eficácia da utilização obrigatória de máscaras de proteção respiratória nas escolas durante o primeiro período do ano letivo 2021–2022.

Conceção Um estudo retrospectivo populacional.

Enquadramento Escolas na Catalunha (Espanha).

População 599 314 crianças com idades compreendidas entre os 3 e os 11 anos que frequentam o pré-escolar (3–5 anos sem obrigatoriedade de uso de máscara) e o primeiro ciclo (6–11 anos com obrigatoriedade de uso de máscara).

Período do estudo De 13 de setembro a 22 de dezembro de 2021 (anterior à variante Ómicron).

Intervenções Uma comparação quase experimental entre as crianças no último ano do pré-escolar (5 anos), como grupo de controlo, e crianças no 1º ano do primeiro ciclo (6 anos) como grupo intervencional.

Medidas do desfecho principal Incidência de SARS-CoV-2, taxa de ataques secundários (SAR) e número reprodutivo efetivo (R^*).

Resultados A incidência de SARS-CoV-2 foi significativamente mais baixa no pré-escolar do que no primeiro ciclo, e foi observada uma tendência crescente com a idade. As crianças de 6 anos de idade apresentaram uma maior incidência do que as de 5 anos [3,54% vs 3,1% OU 1,15 (IC 95%, 1,08 a 1,22)] e uma SAR ligeiramente mais baixa, ainda que estatisticamente não relevante [4,36% vs. 4,59%; risco relativo de incidência 0,96 (IC 95%, 0,82 a 1,11)] e R^* [0,9 vs 0,93; OR 0,96 (IC 95%, 0,87 a 1,09)]. Os resultados mantiveram-se consistentes quando utilizadas as abordagens por método de regressão descontinua e extrapolação de regressão linear.

Conclusões Não encontramos diferenças significativas na transmissão da SARS-CoV-2 devido à obrigatoriedade do uso de máscara nas escolas catalãs. Pelo contrário, a idade foi o fator mais significativo na explicação do risco de transmissão para as crianças que frequentam a escola.

BACKGROUND

Experimental studies have established the efficacy of masks showing 50%–90% reductions in emissions depending on the type of mask.^{1–6} Furthermore, some observational studies have shown that the use of masks can be effective in reducing the transmission of respiratory viruses in certain conditions or settings.^{7–10}

The mandatory use of face covering masks (FCMs) was implemented in many countries, as one of the non-pharmaceutical interventions (NPIs) aimed at preventing the transmission of the SARS-CoV-2 during the COVID-19 pandemic. In addition, some countries extended FCM mandates to schools despite the European Centre for Disease Prevention and Control and WHO

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Only laboratory or observational studies have been performed to explore the effect of face covering masks (FCMs) or its mandate in preventing COVID-19 transmission in schools.
- To date, there have been no randomised controlled trials on the FCM mandate in schools.
- There is a lack of scientific evidence supporting the decision to make FCM mandatory for children over 5 years of age.

WHAT THIS STUDY ADDS

- We used a quasi-experimental design to study the effectiveness of the FCM mandate, comparing the outcome between children with FCM and children without.
- The differences in secondary attack rate (SAR) or R^* between children attending the last preschool year (P5) and children in the first year of primary education were not statistically significant.
- Age dependency is key for understanding SARS-CoV-2 transmission with the Delta variant, reinforcing the same outcome that was observed with previous SARS-CoV-2 variants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- FCM mandate for children attending school is based on insufficient scientific evidence.

only recommended their use for children over 12, or in situations where community transmission is high.^{11 12}

COVID-19 is less severe in children probably due to several age-related factors in innate and adaptive immune response.^{13–19} Recent studies about the effectiveness of FCM mandates in educational settings show mixed results.^{20 21} Some of these studies have used an ecological design, and their findings may have been affected by various limitations and confounders.

In Catalonia (Spain), schools include children between 3 and 12 years old. Despite education not

being mandatory until 6, almost all children between 3 and 5 years old go to school and share the same building or educational space with older children. After school closures in March 2020, schools reopened in September 2020 for face-to-face classes with some NPI including FCM (mandatory for 6 years and older) and bubble groups with a fixed and stable number of students and teachers. The whole bubble group was quarantined and tested whenever a positive case was detected.²² A study performed during the first term of the 2020–2021 academic year showed an age dependency on SARS-CoV-2 transmission in schools.²³ At the beginning of the first school term of 2021–2022, before the Omicron wave, Delta was the most prevalent variant, vaccination coverage was 92% for teachers, and children under 12 were not yet eligible for vaccination.²⁴ This situation allowed us to perform a quasi-experimental study for analysing the effectiveness of the FCM mandate in schools.

We analysed routinely collected health data to compare the incidence of SARS-CoV-2, secondary attack rates (SARs) and the effective reproductive number (R^*) among school children, comparing those without mandatory FCM (3–5 year olds) and those with FCM (6–11 year olds) during the first term of the school year 2021–2022, to assess the effect of FCM mandates on SARS-CoV-2 transmission within schools.

METHODS

Study design and data sources

A retrospective population-based cohort study was designed using data from the official census of school age children in Catalonia linked to the regional central database of reverse transcriptase PCR (RT-PCR) and lateral flow tests (LFTs) for SARS-CoV-2. During the whole study period, each time a positive case was detected by the health system, the whole bubble group was immediately quarantined for a 10-day period, and all children were tested with an RT-PCR 4–6 days after their last contact with the initial case, with a recommendation of a second test if symptoms appeared despite a negative test result.

Participants, cohorts and follow-up

The study population was a cohort of children aged between 3 and 11 years assigned to a stable bubble group according to the 2021–2022 academic census from the Catalan Department of Education. We excluded those with either more than 30 or less than five members, to ensure better intra-group stability. We also excluded schools that did not have bubble groups for all nine academic years, to ensure similar in-school protocols for both cohorts.

We used data from the first term of the 2021–2022 academic year (13 September to 22 December 2021) for the purposes of recruiting, and allowed for 10 more days (until 1 January 2022) for the occurrence of possible secondary cases for SAR and R^* calculations.

We defined an index case as the first case in a bubble group in a 10-day window, and secondary cases were defined, according to Catalan SARS-CoV-2 guidelines, as any case testing positive within the 10 days following an index case in their bubble group. A student testing positive after this 10-day period was considered as a new index case.

Analyses were performed at bubble group and academic year levels. Groups were analysed by school year, three in the preschool stage (P3, P4 and P5 according to the age of the students in each group) and six in the primary education stage (years 1–6, ages 6–11 years). In Catalonia, preschool and primary education children share the same school buildings, while kindergarten is only for younger children (under 3 years).

Our main analysis was the comparison of the epidemiological variables between children at P5 year and children at year 1 of primary education. The only difference between them, regarding NPI, was the FCM mandate: children at P5 without the mandatory use of FCM and children at year 1 of primary education with mandatory use of FCM. To contextualise, we have also compared the results of the other school years.

Study outcomes and epidemiological measures

The primary outcome was SARS-CoV-2 infection, defined by the date of the first positive RT-PCR or LFT, regardless of the presence of any symptom or clinical diagnosis.

For each school year, we calculated three epidemiological variables:

- Incidence of SARS-CoV-2 infection: as the number of children with a positive test divided by the population.
- SAR: the number of new cases in a bubble group divided by the total number of at-risk group members after subtracting the index case. SAR was calculated for each bubble group, and then summarised for each year as the mean and the median.
- R^* : the average number of secondary cases for each index case as described elsewhere.²³ The average R^* was calculated for all bubble groups within each school year.

Statistical analysis

For descriptive analysis, we expressed continuous variables as mean (SD) or median (IQR) and summarised categorical variables as number (percentage). We calculated a 95% CI for SARS-CoV-2 incidence and SAR. We used a logistic regression model to estimate the OR and 95% CI of SARS-CoV-2 incidences and a negative binomial model to estimate the incidence risk ratio (IRR) and 95% CI of SAR between the P5 school year, and the first year of primary education. From the distribution of cases, we fitted a negative binomial distribution to obtain the mean (R^*) and the 95% CI from the SD.

In addition, we performed a regression discontinuity design (RDD) analysis for incidence considering age instead of grade, as a part of a post hoc analysis. Finally, we ran a simulation analysis assuming that the age trend observed in previous studies²³ is a parameter that should be maintained in our data across the different grades (see online supplemental material for further details of both analyses).

We used R V.4.0.0 and MATLAB V.2021b for the analyses.

RESULTS

A total of 1907 schools, 28 575 bubble groups and 599 314 (94.7%) pupils were included in the analysis after the exclusions (figure 1).

The number of SARS-CoV-2 infections during the study period was 24 762 (4.13%). Table 1 summarises the number of students, bubble groups and SARS-CoV-2 infections for each school year.

Figure 2 shows the 7-day moving average of SARS-CoV-2 infections by school year. We observed that all school years follow a similar pattern, and preschool years were consistently less infected than older children. Incidence was lower in preschool stage than in primary education, ranging between 1.74% in P3 and 5.91% in year 6 of primary education (table 2).

We analysed 13 404 outbreaks during the study period. On average, 57% had no secondary cases, but there were more outbreaks without secondary cases in preschool (70%) than in primary education (53%) (table 1). Median SAR was 0 in all years except for year 6 of primary education (table 2). Figure 3 shows the mean SAR by school year. While lower values were observed in preschool (2.34%, 2.77% and 4.59% in P3, P4 and P5, respectively), the highest value was in year 6 of primary education, with a mean SAR of 7.17%. The same pattern was observed for R^* , highlighting the low values in preschool P3 and P4 and the $R^* > 1$ for years 3, 4, 5 and 6 of primary education (figure 3).

Our main analysis shows that SARS-CoV-2 incidence and the percentage of positive tests were significantly higher for year 1 of primary education than in P5: incidence was 3.54% vs 3.1%, with an OR of 1.15 (95% CI 1.08 to 1.22); and test positivity was 7.98% (95% CI 7.69% to 8.27%) and 6.82% (95% CI 6.55% to 7.10%), respectively. Conversely, SAR and R^* were similar for both years. Median SAR was 0, and mean SAR was slightly lower—but not statistically significant—in year 1 of primary education than in P5, 4.36% vs 4.59%, respectively (IRR 0.96 (95% CI 0.82 to 1.11)). Furthermore, R^* was not significantly lower for year 1 of primary education either: 0.90 vs 0.93 (OR 0.96 (95% CI 0.87 to 1.09)) (see table 2 and figure 3). Additionally, the RDD analysis found

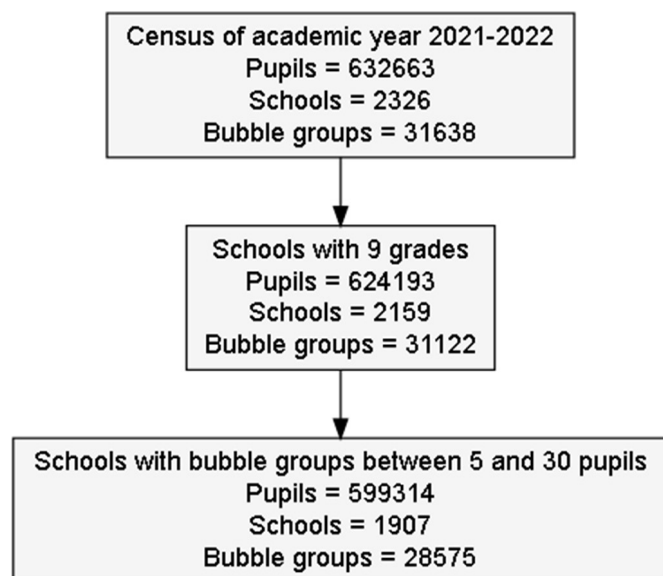


Figure 1 Population flow chart.

a non-statistically significant absolute difference of -0.0089% (p value 0.930); and the simulation analysis extrapolating the regression from primary education rendered expected values for incidence, SAR and R^* in P5 not significantly different from the observed (online supplemental material).

DISCUSSION

The main findings of the study show no significant differences for children in the last grade of preschool (P5) and the first year of primary education in COVID-19 transmission indicators during the study period, despite their difference in FCM mandate and the strong age dependency of transmission of SARS-CoV-2 in schools. This reinforces the results published for the year 2020–2021, but with a more transmissible SARS-CoV-2 Delta variant.²³

The age trend observed for P5 and older children follows a different pattern when P3 and P4 are included in the analysis. With no mandatory use of FCM, the youngest children have significantly lower transmission indicators when compared with any other group. These findings may be related to the age decrease trend of the innate or adaptive immunological response, and a shift towards an adult-like immunological response pattern as the child enters primary school as had already been described.^{13–17} Finally, as primary infection with several human coronaviruses typically occurs early in childhood, higher production of cross-reactive T cells in younger children is to be expected.^{18–25} This might explain the low intraclass transmission of the SARS-CoV-2 found here and in some studies.²⁶

Despite no significant differences between P5 and year 1 of primary education being found in transmission indicators, the

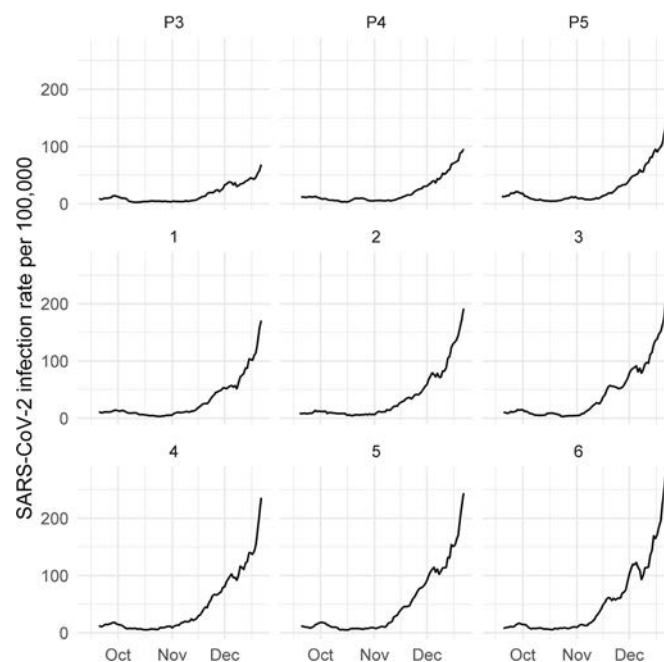


Figure 2 The 7-day moving average of daily SARS-CoV-2 infection rates per 100 000 population by school year (P3–P5 for preschool, and years 1–6 for primary education).

extrapolation analysis of SAR and R^* from primary education suggests transmission was slightly higher than expected in P5, although non-statistically significant. This could be explained by different classroom dynamics that may involve closer contact between the younger children, and by the lower test positivity in P5 compared with primary education suggesting a greater diagnostic effort.

Other studies that found some effects of FCM have certain limitations due to their ecological design, with no distinction between children and adolescents in their analyses, or to not taking differences in staff vaccination status or testing rate into account.^{20–27} It should be noted that substantial reductions in transmission have only consistently been detected in laboratory settings and in tightly controlled environments.^{4–9–10} However, our results are similar to other studies analysing the impact of mask-wearing policies for students in educational settings.^{28–29}

Our study has certain limitations. We performed an intention-to-treat analysis. This means that there may have been children in P5 who did use FCM, and also children in year 1 of primary education who used them incorrectly. However, the aim of our study was not to measure the individual effectiveness of FCM, but to evaluate the effectiveness of mask mandates in the real-world context of schools. Although both cohorts were balanced at territorial and socioeconomic levels given the study design, there may be

Table 1 Number of students, bubble groups and SARS-CoV-2 infections by grade in Catalan schools (including preschool and primary grades)

School year	Mean age (SD)	Students (n)	Bubble groups	Cases from 13 September to 22 December 2021	Index cases (outbreaks)	Secondary cases	% of outbreaks without secondary cases
P3	3.1 (0.3)	54 210	2932	942	724	307	75.3
P4	4.0 (0.2)	60 094	2994	1388	976	526	72.7
P5	5.0 (0.3)	63 344	3040	1966	1133	1052	64.2
1	6.0 (0.2)	66 204	3148	2346	1405	1269	61.3
2	7.0 (0.2)	67 455	3186	2781	1569	1566	56.3
3	8.1 (0.3)	66 614	3131	3074	1638	1877	53.1
4	9.0 (0.3)	71 590	3292	3703	1879	2436	52.6
5	10.1 (0.3)	73 702	3349	4062	2029	2611	51.0
6	11.0 (0.3)	76 101	3503	4500	2051	3092	48.8
Preschool education (P3–P5)		177 648	8966	4296	2833	1885	70.0
Primary education (years 1–6)		421 666	19 609	20 466	10 571	12 851	53.3
Total		599 314	28 575	24 762	13 404	14 736	56.8

Table 2 SARS-CoV-2 incidence, secondary attack rate (SAR), effective reproductive number (R^*) and percentage of positive tests by school year

Year (age in years)	SARS-CoV-2 incidence (95% CI)	SAR Mean (SD)	SAR Median (IQR)	R^* (95% CI)	% of positive tests (95% CI)
P3 (3)	1.74% (1.63 to 1.85)	2.34% (5.53)	0.00 (0.00–0.00)	0.42 (0.35 to 0.49)	3.26 (3.06 to 3.45)
P4 (4)	2.31% (2.19 to 2.43)	2.77% (6.55)	0.00 (0.00–4.17)	0.54 (0.46 to 0.61)	4.89 (4.65 to 5.12)
P5 (5)	3.10% (2.97 to 3.23)	4.59% (9.30)	0.00 (0.00–5.00)	0.93 (0.82 to 1.04)	6.82 (6.55 to 7.10)
1 (6)	3.54% (3.40 to 3.68)	4.36% (8.38)	0.00 (0.00–5.00)	0.90 (0.81 to 0.99)	7.98 (7.69 to 8.27)
2 (7)	4.12% (3.97 to 4.27)	4.92% (8.95)	0.00 (0.00–5.88)	1.00 (0.91 to 1.08)	8.67 (8.38 to 8.96)
3 (8)	4.61% (4.45 to 4.77)	5.57% (9.52)	0.00 (0.00–7.62)	1.15 (1.05 to 1.24)	9.09 (8.80 to 9.37)
4 (9)	5.17% (5.01 to 5.33)	6.10% (9.76)	0.00 (0.00–8.33)	1.30 (1.20 to 1.39)	10.02 (9.74 to 10.31)
5 (10)	5.51% (5.35 to 5.67)	6.06% (9.86)	0.00 (0.00–8.33)	1.29 (1.20 to 1.38)	9.55 (9.29 to 9.81)
6 (11)	5.91% (5.74 to 6.08)	7.17% (11.8)	3.85 (0.00–9.09)	1.51 (1.40 to 1.61)	10.36 (10.09 to 10.63)

other variables that were not considered (ie, classroom dynamics or the density of students in the classroom). Besides, we are probably over-reporting the study outcomes because we do not distinguish possible concomitant cases in a 10-day window. In addition, a higher percentage of asymptomatic infections in younger children might produce reduced detection of single individual asymptomatic cases, but huge diagnostic efforts to detect secondary infections have been in place since the previous academic year.³⁰ Finally, although quasi-experimental designs lack the randomised controlled trial (RCT) ability to equally distribute confounding between groups, they are a better approach than other designs commonly used in this field.

During the study period, Delta was the most prevalent SARS-CoV-2 variant. However, at the beginning of January 2022, Omicron became the dominant variant (>95% on 5 January 2022 according to Catalan authorities). At the beginning of the second term (10 January 2022), 7-day cumulative COVID-19 per 100 000 inhabitants was 2391.6 (see official Catalan website about COVID-19: <https://dadescovid.cat/?lang=eng>). That could affect the odds to find a secondary case that in fact is a concomitant case. In addition, school guidelines were the same during the analysed term but changed for the second term of the academic year 2021–2022. Finally, the vaccination campaign for children between 5 and 11 years was launched at the end of December 2021. Data from the second term are thus not comparable to the data analysed in our article. Nevertheless, it is unlikely that the effectiveness of the mask mandate measure will increase with a more transmissible variant.

This study also has strengths. We analysed two homogeneous cohorts (P5 and year 1 of primary education), the latter with mandatory use of FCM, acting as an interventional group, and the former without, as a control group. We do not expect to find great differences in the host response due to the age or in the behaviour between both grades that could influence the results obtained, although it should be considered that classroom dynamics may be different. Given the difficulty of conducting RCT in educational settings, this quasi-experimental analysis is the best possible approach to the aim of the study. In addition, the analysis of the rest of the years of primary education shows an age-dependency increase trend for all the epidemiological measures, suggesting that age is an important component. This is consistent with the findings of a study performed with data from the first term of the previous academic year and different SARS-CoV-2 variant.²³ Finally, our results are consistent using different statistical approaches.

In conclusion, FCM mandates in schools showed no significant differences in terms of transmission. Conversely, we found that age is a key component explaining transmission in children. Considering the non-effectiveness of FCM mandates found in our quasi-experimental approach, and the negative impact on children's health of some measures implemented to mitigate transmission, such as school closures,^{31 32} policymakers should ensure that all measures within schools are evaluated (including school closures, home schooling, bubble groups, ventilation, test and trace, etc), and that the risks and benefits of such interventions are balanced.

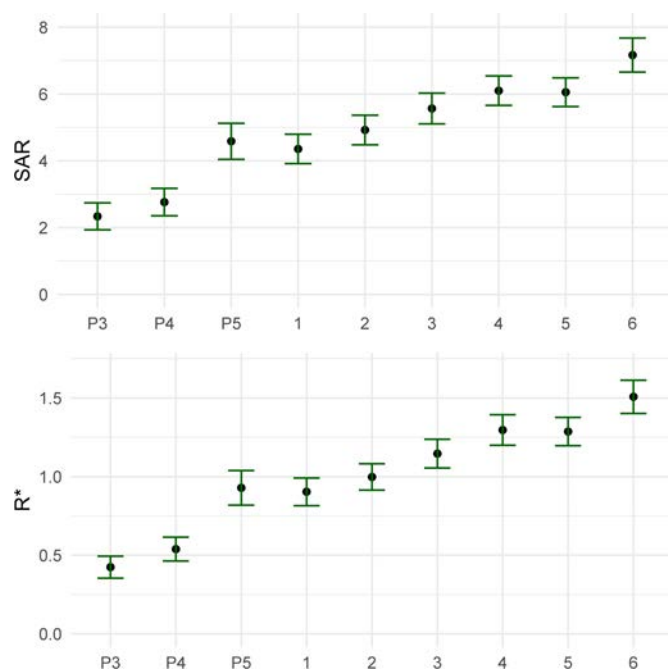


Figure 3 Mean secondary attack rate (SAR) and effective reproductive number (R^*) with 95% CI by school year (P3–P5 for preschool and years 1–6 for primary education).

Author affiliations

¹Sistemes d'Informació dels Serveis d'Atenció Primària (SISAP), Institut Català de la Salut, Barcelona, Catalonia, Spain

²Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

³Department of Physics, Universitat Politècnica de Catalunya, Barcelona, Catalonia, Spain

⁴IDIA Jordi Gol, Barcelona, Catalonia, Spain

⁵Departament de Salut, Generalitat de Catalunya, Barcelona, Catalonia, Spain

⁶Equip Pediàtric Territorial Alt Penedès-Garraf, Institut Català de la Salut, Barcelona, Catalonia, Spain

⁷ISGlobal, Hospital Clínic—Universitat de Barcelona, Barcelona, Catalonia, Spain

⁸Centro de Investigación em Saúde de Manhica, Manhica, Maputo, Mozambique

⁹Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

¹⁰Pediatrics Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Esplugues (Barcelona), Catalonia, Spain

¹¹CREA, Catalan Institution for Research and Advanced Studies, Barcelona, Catalonia, Spain

¹²Direcció Assistencial d'Atenció Primària i a la Comunitat, Institut Català de la Salut, Barcelona, Catalonia, Spain

¹³Paediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain

¹⁴Department of Infectious Diseases, Vall d'Hebron Research Institute, Barcelona, Catalonia, Spain

Twitter Ermengol Coma @ErmengolComa, Leonardo Méndez-Boo @LMBooster, Sergio Alonso @SergioAlonsoMun, Eduardo Hermsilla @eduboniqueta, Enric Alvarez-Lacalle @kilocurie, David Pino @pino_in_bcn, Laia Asso @laia_asso, Anna Gatell @GatellAnna, Antoni Soriano-Aranda @tonisoriano66 and Clara Prats @prats_clara

Acknowledgements To the Spider's web translator web, and especially to Cristina Roman and Jane Perkins for their English style review of the manuscript.

Contributors EC, SA, AS-A, FF and CP: Conceptualisation. EC, MC, LM, SA, EH, FF and CP: Methodology. EC, MC, LM, SA, EH, AS-A, FF and CP: Validation. EC, MC, LM, SA, EH, FF and CP: Formal analysis. EC, LM, EH, AM, MM, LA and FF: Resources. EC, MC, LM, SA, EH, EA-L, DP, QB, AS-A, FF and CP: Writing—original draft preparation. All authors: Visualisation. EC, SA, AS-A, FF and CP: Supervision. CP, EC: Guarantors.

Funding CP and SA received funding from Ministerio de Ciencia, Innovación y Universidades and FEDER, with the project PGC2018-095456-B-I00. AS-A received funding from the Generalitat de Catalunya, with the project Sentinel Schools.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was evaluated and approved by the Clinical Research Ethics Committee of the IDIA Jordi Gol, Reference 21/018-PCV. This research was based on the agreement established in Regulation 2016/679 of the European Parliament and the Council of Europe of 27 April 2016 on Data Protection, and Organic Law 3/2018 of December 5 on the protection of personal data and the guarantee of digital rights.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any

reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This article is made freely available for personal use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iDs

Ermengol Coma <http://orcid.org/0000-0001-8000-3321>
 Martí Català <http://orcid.org/0000-0003-3308-9905>
 Leonardo Méndez-Boo <http://orcid.org/0000-0002-9215-4378>
 Sergio Alonso <http://orcid.org/0000-0002-3989-8757>
 Eduardo Hermosilla <http://orcid.org/0000-0002-3031-0304>
 Enric Alvarez-Lacalle <http://orcid.org/0000-0001-6824-6857>
 David Pino <http://orcid.org/0000-0002-4512-0175>
 Manuel Medina <http://orcid.org/0000-0002-2791-5847>
 Laia Asso <http://orcid.org/0000-0002-1539-3543>
 Anna Gatell <http://orcid.org/0000-0003-4930-6994>
 Quirque Bassat <http://orcid.org/0000-0003-0875-7596>
 Ariadna Mas <http://orcid.org/0000-0001-5336-7533>
 Antoni Soriano-Arandes <http://orcid.org/0000-0001-9613-7228>
 Francesc Fina Vilés <http://orcid.org/0000-0001-7106-5635>
 Clara Prats <http://orcid.org/0000-0002-1398-7559>

REFERENCES

- van der Sande M, Teunis P, Sabel R. Professional and home-made face masks reduce exposure to respiratory infections among the general population. *PLoS One* 2008;3:e2618.
- Balazy A, Toivola M, Adhikari A, et al. Do N95 respirators provide 95% protection level against airborne viruses, and how adequate are surgical masks? *Am J Infect Control* 2006;34:51–7.
- Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. *Nat Med* 2020;26:676–80.
- Cappa CD, Asadi S, Barreda S, et al. Expiratory aerosol particle escape from surgical masks due to imperfect sealing. *Sci Rep* 2021;11:12110.
- Chan JF-W, Yuan S, Zhang AJ, et al. Surgical mask partition reduces the risk of noncontact transmission in a golden Syrian hamster model for coronavirus disease 2019 (COVID-19). *Clin Infect Dis* 2020;71:2139–49.
- Dbouk T, Drikakis D. On respiratory droplets and face masks. *Physics of Fluids* 2020;32:063303.
- Smith SMS, Sonogoe S, Wallen GR, et al. Use of non-pharmaceutical interventions to reduce the transmission of influenza in adults: a systematic review. *Respirology* 2015;20:896–903.
- Wang Y, Tian H, Zhang L, et al. Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China. *BMJ Glob Health* 2020;5:e002794.
- Payne DC, Smith-Jeffcoat SE, Nowak G, et al. SARS-CoV-2 Infections and Serologic Responses from a Sample of U.S. Navy Service Members - USS Theodore Roosevelt, April 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:714–21.
- et al Kim MS, Seong D, Han L. Comparative efficacy of N95, surgical, medical, and non-medical face masks in protection of respiratory virus infection: a living systematic review and network meta-analysis. Available: <https://ssrn.com/abstract=3768550>
- European Centre for Disease Prevention and Control. Questions and answers on COVID-19: children aged 1 – 18 years and the role of school settings. Available: <https://www.ecdc.europa.eu/en/covid19/questions-answers/questions-answers-school-transmission> [Accessed 08 Sep 2021].
- World Health Organization & United Nations Children's Fund (UNICEF). Advice on the use of masks for children in the community in the context of COVID-19: annex to the advice on the use of masks in the context of COVID-19. Available: <https://apps.who.int/iris/handle/10665/333919> [Accessed 08 Sep 2021].
- Neeland MR, Bannister S, Clifford V, et al. Children and adults in a household cohort study have robust longitudinal immune responses following SARS-CoV-2 infection or exposure. *Front Immunol* 2021;12:741639.
- Yoshida M, Worlock KB, Huang N, et al. Local and systemic responses to SARS-CoV-2 infection in children and adults. *Nature* 2022;602:321–7.
- Vono M, Huttner A, Lemeille S, et al. Robust innate responses to SARS-CoV-2 in children resolve faster than in adults without compromising adaptive immunity. *Cell Rep* 2021;37:109773.
- Loske J, Rohmel J, Lukassen S, et al. Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. *Nat Biotechnol* 2022;40:319–24.
- Bonfante F, Costenaro P, Cantarutti A, et al. Mild SARS-CoV-2 infections and neutralizing antibody titers. *Pediatrics* 2021;148:e2021052173.
- Dowell AC, Butler MS, Jinks E, et al. Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. *Nat Immunol* 2022;23:40–9.
- Zimmermann P, Curtis N. Why does the severity of COVID-19 differ with age?: understanding the mechanisms underlying the age gradient in outcome following SARS-CoV-2 infection. *Pediatr Infect Dis J* 2022;41:e36–45.
- Budzyn SE, Panaggio MJ, Parks SE, et al. Pediatric COVID-19 Cases in Counties With and Without School Mask Requirements - United States, July 1–September 4, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1377–8.
- Nelson SB, Dugdale CM, Bilinski A. Prevalence and risk factors for in-school transmission of SARS-CoV-2 in Massachusetts K–12 public schools 2020–2021. *medRxiv* 2021.
- Generalitat de Catalunya. Mesures extraordinàries de Salut per evitar ELS brots de la COVID-19 a les escoles. Available: https://educacio.gencat.cat/web/shared/continguts_per_compartir/ENS/salut-escola/documentacio/families/20200902-carta-families.pdf [Accessed 01 Feb 2022].
- Alonso S, Alvarez-Lacalle E, Català M, et al. Age-Dependency of the propagation rate of coronavirus disease 2019 inside school bubble groups in Catalonia, Spain. *Pediatr Infect Dis J* 2021;40:955–61.
- Comitè Científic Assessor de la Covid-19. Generalitat de Catalunya. Posició del CCAC sobre la retirada de les mascaretes en espais exteriors en l'mbit escolar. Available: https://salutpublica.gencat.cat/web/contenut/minisite/aspacat/sobre_l'agencia/comite_assessor_covid19/1243-ASPCAT-Posicionament-CCAC-retirada-mascaretes-espais-exteriors-04-11-2021-plantilla.pdf [Accessed 01 Feb 2022].
- Brodin P. SARS-CoV-2 infections in children: understanding diverse outcomes. *Immunity* 2022;55:201–9.
- Buonsenso D, De Rose C, Moroni R, et al. SARS-CoV-2 infections in Italian schools: preliminary findings after 1 month of school opening during the second wave of the pandemic. *Front Pediatr* 2020;8:615894.
- Jehn M, McCullough JM, Dale AP, et al. Association Between K-12 School Mask Policies and School-Associated COVID-19 Outbreaks - Maricopa and Pima Counties, Arizona, July–August 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1372–3.
- Oster E, Jack R, Halloran C. COVID-19 mitigation practices and COVID-19 rates in schools: report on data from Florida, New York and Massachusetts. *medRxiv* 2021:2021.05.19.21257467.
- Department of Education UK. Evidence summary. coronavirus (COVID-19) and the use of face coverings in education settings, 2022. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1055639/Evidence_summary_-_face_coverings.pdf [Accessed 02 Feb 2022].
- Perramon A, Soriano-Arandes A, Pino D, et al. Schools as a framework for COVID-19 epidemiological surveillance of children in Catalonia, Spain: a population-based study. *Front Pediatr* 2021;9:754744.
- Buonsenso D, Roland D, De Rose C, et al. Schools closures during the COVID-19 pandemic: a catastrophic global situation. *Pediatr Infect Dis J* 2021;40:e146–50.
- Bonal X, González S. The impact of lockdown on the learning gap: family and school divisions in times of crisis. *Int Rev Educ* 2020;66:635–55.

BMJ Case Reports

BMJ Case Reports helps you to easily find clinically important information on common and rare conditions. Including the largest single collection of case reports online, this is an essential resource to keep your education up to date.

Become a Fellow to:

- **Quickly find** the cases that interest you most from around the globe
- **Learn from real cases** and use any of our published case reports in your teaching
- Submit your own cases with **rapid publication and supportive peer review**
- **Access content in a way that suits you** with our articles, videos, images and blogs



Join our online communities:

[@BMJCaseReports](https://twitter.com/BMJCaseReports) [f/BMJCaseReports](https://facebook.com/BMJCaseReports)



Find out more
casereports.bmj.com

Influência das epidemias e das pandemias na utilização dos SU pediátricos: uma revisão sistemática

Damian Roland,^{1,2} Adam Gardiner,³ Darakhshan Razzaq,⁴ Katy Rose,^{5,6} Silvia Bressan,⁷ Kate Honeyford,⁸ Danilo Buonsenso,^{9,10} Liviana Da Dalt,⁷ Tisham De,¹¹ Ruth Farrugia,¹² Niccolo Parri,¹³ Rianne oostenbrink,¹⁴ Ian K Maconochie,⁵ Zsolt Bognar,¹⁵ Henriette A Moll,¹⁴ Luigi Titomanlio,¹⁶ Ruud Gerard Gerard Nijman,^{5,17} in association with the REPEM network (Research in European Paediatric Emergency Medicine) as part of the EPISODES Study

► Additional supplemental material is published online only. To view, please visit the journal online <http://dx.doi.org/10.1136/archdischild-2022-324108>

For numbered affiliations see end of article.

Correspondence to Professor Damian Roland, Health Sciences, University of Leicester, Leicester, UK; dr98@leicester.ac.uk

Received 8 March 2022
Accepted 5 September 2022
Published Online First
26 September 2022

RESUMO

Objetivo Para avaliar o impacto das epidemias e pandemias na utilização dos serviços de urgência pediátrica para obter aconselhamento ao nível das políticas de saúde.

Enquadramento Revisão sistemática.

Conceção Foram realizadas pesquisas na Medline, EMBASE, CINAHL, Scopus, Web of Science e Cochrane Library para estudos que relatavam alterações na utilização dos serviços de urgência pediátrica durante a epidemia (tal como foi definido pela OMS).

Pacientes Crianças com menos de 18 anos.

Intervenções Foi utilizada uma ferramenta de avaliação de qualidade do National Institutes of Health para estudos de coorte observacional e transversal.

Medidas do desfecho principal Alterações na utilização dos serviços de urgência pediátrica.

Resultados Foram incluídos 131 artigos nesta revisão, 80 % dos quais avaliaram o impacto da COVID-19. Os estudos que analisam o COVID-19, SARS, Síndrome Respiratório do Médio Oriente (MERS) e Ébola constatarem uma redução das visitas ao serviço de urgência pediátrico (SUP), ao passo que os estudos relativos a surtos de H1N1, vírus chicungunha e *Escherichia coli* constatarem um aumento das visitas ao SUP. No caso da COVID-19, houve uma redução de 63,86 % (IC 95%, 60,4 a 67,31%) com um intervalo de -16,5% a -89,4%. A síntese dos resultados sugere que o medo das doenças epidémicas, seja de as contrair ou dos seus desfechos clínicos potencialmente adversos, resultou em reduções e aumentos na utilização do SUP, respetivamente.

Conclusões A escala e direção do efeito da utilização do SUP depende tanto da doença epidémica, como das medidas de saúde pública implementadas e de como estas influenciam a tomada de decisão. Os decisores políticos têm de estar atentos ao modo como o receio de um vírus entre a população em geral pode influenciar a sua resposta aos conselhos de saúde pública. Existe uma grande desigualdade no relato do impacto epidémico na utilização do SUP que tem de ser abordado.

Número de registo do ensaio CRD42021242808.

INTRODUCTION

The uncertainty surrounding the infectivity and mortality rates of COVID-19 meant many countries instituted restrictions on public freedoms to drive down community transmission. The use of strict lockdowns and 'stay-at-home' orders have been under scrutiny, especially as many of these countries recorded drastic reductions in the utilisation of their emergency healthcare services by patients without COVID.¹ It has become clear that other than the rare complication of multi-system inflammatory syndrome in children,² SARS-CoV-2 infection in children is generally a mild disease.³ However, there was also early

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- There have been five previous disease outbreaks, since 2005, which have been classified as a 'Public Health Emergency of International Concern' by WHO.
- The evidence of their impact on emergency services for children has not been subject to a formalised review.

WHAT THIS STUDY ADDS

- This systematic review demonstrates that pandemics have significantly different impacts on paediatric emergency service utilisation depending on the epidemic/pandemic.
- Differences in impact within and between countries may be related to the number of publications from that country and the length of time of their studies.
- The reasons for changing emergency care utilisation are likely related to the public health response and parent/carer concern about the severity of the disease process.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Policy makers must be aware how fear of viruses among the general public may influence their response to public health advice.
- The inequality between low-middle and high-income countries in reporting the impact of emergency service utilisation for children must be recognised and addressed.



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Roland D, Gardiner A, Razzaq D, et al. Arch Dis Child 2023;108:115–122.

The aim of this study was to conduct a systematic review of the literature from across the world on the impact pandemics and epidemics had on the utilisation of emergency care services by children.

METHODS

This work is part of the EPISODES study, an international retrospective cohort study looking at the epidemiology, severity and outcomes of children presenting to emergency departments across Europe during the SARS-CoV-2 pandemic.⁷

This review has followed the guidance published within the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁸

The predefined study characteristics and full search strategy are set out in the form of a 'PICO grid' in online supplemental appendix A, table A and, where possible, the search was limited to 'child <18 years' and 'English language'. A senior academic librarian (information specialist) specialising in medical research reviewed the search strategy.

Two reviewers performed the title and abstract screening with any conflicts resolved by a third reviewer. Criteria for inclusion were original studies examining the access to emergency care services by children (<18 years) during pandemics/epidemics as defined by WHO (<https://www.who.int/emergencies/diseases/en/>); studies of adults, 18 years and older were excluded.

To assess the quality of each study, the 'National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies'⁹ was used. A single author (AG) reviewed all papers with the rest of the author group reviewing sections of the selected journals to confirm the answers to the NIH quality assessment tool. The lead author (DR) arbitrated on any differences in quality rating. Due to the heterogeneity between the included articles, meta-analysis could not be performed. Therefore, instead, a narrative analysis of the articles, split by epidemic disease being studied, was conducted.

We registered the protocol of our systematic review with PROSPERO (www.crd.york.ac.uk/PROSPERO, published on 16 March 2021, protocol ID: CRD42021242808). The finalised protocol can be found in online supplemental appendix 2.

RESULTS

The literature search produced a total of 9374 results; deduplication removed 1806 articles.

A total of 7568 articles were screened through the title and abstract review. There was unanimous decision to exclude 7169 of the articles and a further 198 articles with conflicting decisions were excluded by the third reviewer.

The 124 articles that were included after the full-text review were searched for additional potentially includable articles within their references. Seven previously not retrieved articles met

the inclusion criteria and therefore 131 articles entered the data extraction phase and final analysis. A PRISMA flowchart summarising this process can be found in figure 1.

Of the 131 articles included for final analysis and review, 104 (79.4%) were publications related to the COVID-19 pandemic only^{10–112}; 16 articles focused on H1N1 (113–128); 4 and 2 articles concerned SARS^{113–116} and MERS,^{117–118} respectively. One article¹¹⁹ had data comparing the effect on children's healthcare utilisation for both the COVID-19 pandemic and SARS outbreak. The final four articles analysed the effect of the Ebola outbreak in Sierra Leone¹²⁰; an outbreak of chikungunya virus in Jamaica in 2014¹²¹; a severe influenza outbreak in Israel in the 1999–2000 season;¹²² and an *Escherichia coli* O157:H7 outbreak in the USA in 1993.¹²³ Analysis of these papers can be found in the online supplemental appendix 3. A world map showing the distribution by country including all the articles can be found in figure 2. It highlights the USA (n=41), Italy (n=25) and the UK (n=9) as major publication countries while also showing the global spread of included articles. Using the World Bank Classification of Countries¹²⁴ shows that the majority of the included articles analysed the effect in 'higher income' countries (n=120 (91.6%)), with only 11 studies (8.4%) from 'upper middle-income countries (UMIC)' (n=6), 'lower middle-income countries (LMIC)' (n=4) and 'lower income' country (n=1).¹²⁰ Online supplemental appendix 4, table B show the study characteristics of the included studies and online supplemental appendix 5, table C show the completed NIH assessment tool for each article.

COVID-19

SARS-CoV-2/COVID-19 was the disease of focus within 105 articles. The majority were published by countries most affected by the disease during the first wave of the pandemic. Most publications were from higher income or upper middle-income countries, with only four papers published from lower middle-income countries: India,^{43–92} Morocco²⁸ and Pakistan.⁷⁹

Initial analysis found that 69 out of 105 (66%) provided quantifiable data for a change in general paediatric emergency department (PED) visits. Collectively, they included about 14 million individual visits, across the various COVID-19 study periods and previous year(s) data (online supplemental table 1). Acknowledging various methodologies were used in studies to compare the observed values with the predicted number for the corresponding time periods, the mean percentage change in PED visits across the 69 included articles was a reduction of 63.86% (95% CI 60.40% to 67.31%) with a range of –16.5% to –89.4.

Figure 3 shows the value for percentage change in PED visits and the number of days included in the study period. There is a suggestion that smaller study periods show a greater reduction, likely

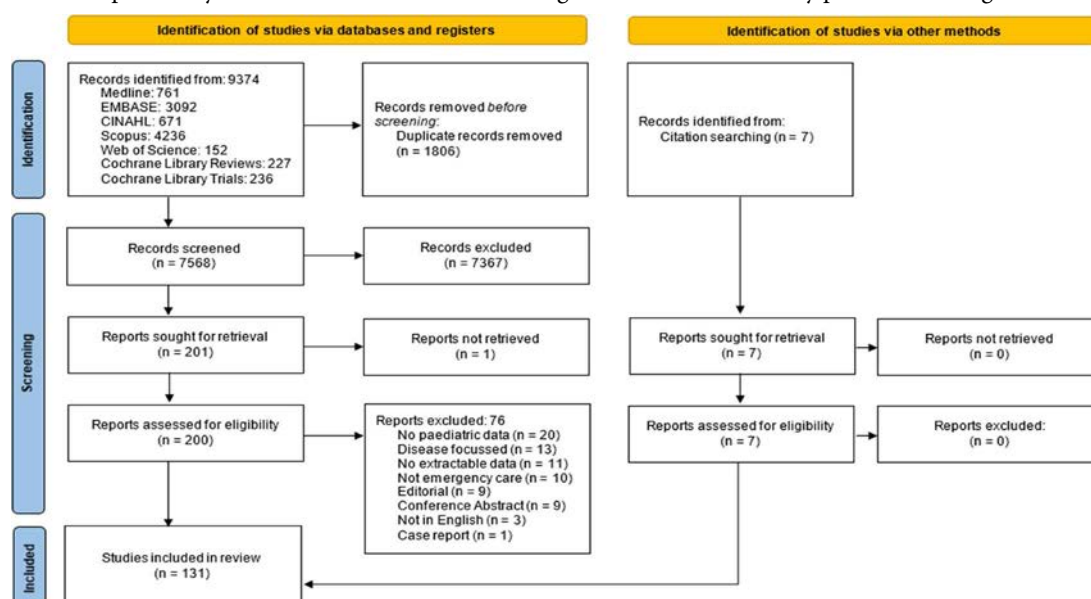


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.⁸

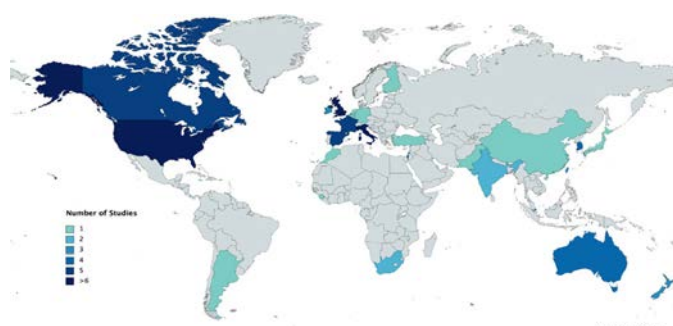


Figure 2 World map showing density of publications by country.

due to studies with shorter study periods focussing on the 'lock-down' period in their respective countries. The difference between countries may also be explained, in part, by the number of papers published in that particular country (figure 4).

Summary data for surgical patients, mental health, diabetes care, specialist healthcare utilisation and qualitative papers can be found in online supplemental appendices 6 and 7, tables D–F with additional analysis into these papers.

Online supplemental appendix 8, table G show the summary data for articles analysing the impact of COVID-19 on PED visits, but it was not possible to retrieve quantitative data from the authors.

Themes were extracted of potential reasons for the reduction in PED visits discussed within the COVID-19 articles (the breakdown by article can be found in online supplemental appendix 4, table B and a summary in online supplemental appendix 9, table H). Twenty-seven papers found no supporting evidence to determine the potential cause for the reduction in visits and, of the remaining 78 papers, the most common reason ($n=52$, 66.7%) alluded to by the authors was the 'fear of contracting the virus', closely followed by the impact of 'social distancing/lockdown measures' ($n=49$, 62.8%).

Influenza A/H1N1 (2009 pandemic)

Sixteen articles that analysed the H1N1 pandemic in 2009/2010 met the inclusion criteria for this review. All were published in higher income countries (11/16 in the USA). The years of publications range from 2009 to 2015, with the most published in 2011 ($n=6$). Eleven^{125–135} of the articles provided data for PED visits for both a period of time during the pandemic and a control period prior to the outbreak. Five^{136–140} did not provide quantifiable data; however, two^{136 137} still provided a percentage change for PED visits and Codish *et al*¹³⁹ analysed the effect of mass media on public behaviour.

During the H1N1 pandemic period, there was a surge in paediatric utilisation of emergency care (summary data can be found in online supplemental appendix 10, table I). The range of values for percentage increase found within the articles is 10.6%–180%.

Sills *et al*¹³¹ postulated multiple reasons for the observed increase in PED visits: parents' fear of adverse outcomes, the perception of

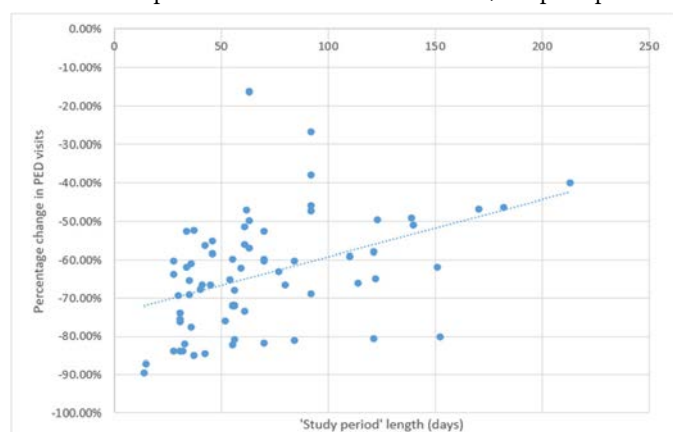


Figure 3 Scatterplot of percentage change in paediatric emergency department (PED) visits by the length in days of the 'study period'. This plot includes data from 69 articles analysing COVID-19 that provided quantitative data for PED visits.

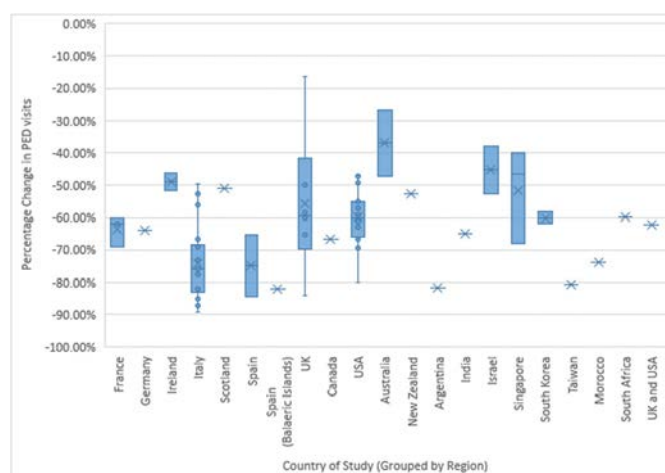


Figure 4 Box and whisker plot showing percentage change in paediatric emergency department (PED) visits by the country of study, grouped by region. This plot includes data from 69 articles analysing COVID-19 that provided quantitative data for PED visits.

less primary care access, inappropriate referrals and advice from the media not being accurate. Codish *et al*¹³⁹ found a significant association between mass media coverage of the H1N1 pandemic in Israel and the number of PED visits.

Severe acute respiratory syndrome (SARS)

There were four articles that analysed the SARS epidemic and each showed a significant reduction in PED visits, ranging from a 36.1% to a 47% reduction. South Korea was the only country to publish articles looking at the 2015 MERS outbreak that met the inclusion criteria for this review. Summary data for SARS articles, as well as MERS articles and the four articles analysing the other epidemic diseases, can be found in online supplemental appendix 11.

Potential reasons for the reductions in PED visits during the SARS epidemic were postulated as a fear of SARS transmission,^{113 114} the influence of media coverage with phrases such as 'killer pneumonia'¹¹³ or public health department advice, in this case, to stay at home when exhibiting SARS-like symptoms.¹¹⁶

DISCUSSION

The evidence presented within this systematic review shows that pandemics/epidemics can result in changes in emergency care utilisation both directly (ie, the causative organism results in ill health and a need to present to emergency services) and indirectly (attendance to emergency care may be reduced because of fear of catching a disease from other patients) dependent on the specific epidemic disease.

A critical finding was the disproportionate nature of research in this area both in relation to the country of research and the epidemic/pandemic. The proportion of articles addressing the effects of COVID-19 was large, accounting for 80% of the articles, with a significant proportion of these being from high-income countries. Fontelo and Liu¹⁴¹ reviewed recent publication trends from countries and found 30 countries generated 94.6% of all publications and 98.1% of publications in core clinical journals worldwide. Of further note is that for COVID-19, two papers published in India,^{43 92} one published in Pakistan⁷⁹ and another in Morocco²⁸ all show similar changes in healthcare utilisation to the rest of the included articles, implying that the observed indirect effects of the COVID-19 pandemic were not less severe, nor magnified in high-income countries. However, this assertion is severely limited by the fact that it only draws on evidence from 4 of 105 papers and only 2 of these papers provide data for general ED visits: Raman and Madhusudan⁴³ and Mekaoui *et al*.²⁸ This disparity of evidence between high-income and low-middle-income countries has implications for the extension of early research findings from future pandemics, as it cannot be assumed that low-income and middle-income countries' emergency service utilisation will be similar to early reports from high-income countries. Of particular

significance is the very small amount of information available for diseases such as Ebola and chikungunya.

This systematic review shows that for the COVID-19 pandemic, the 2015 MERS outbreak, the 2003 SARS pandemic, the 2014 Ebola outbreak and the 1999–2000 influenza outbreak in Israel, there were significant decreases in paediatric utilisation of emergency care services. These decreases were most noticeable throughout the COVID-19 pandemic, with evidence showing that the institution of lockdowns and home confinements coincided with a sudden drop in PED visits.^{10 11 13 76}

Low acuity attendances to emergency services occur commonly in high-income countries.^{142 143} Our review generally found either a larger reduction in lower acuity paediatric patients compared with those requiring more urgent care, resulting in a proportional increase in higher acuity paediatric patients,^{35 36 41 43 56 102} or no change in the overall proportion,^{64 66 73} despite overall reduced numbers. Individual studies with specific triage detail³⁴ have shown a large decrease in absolute numbers for non-urgent (Emergency Severity Index (ESI) 4 or 5) but a proportional increase in urgent (ESI 3) visits or a large proportional and significant absolute increase in resuscitation/emergency consultations. The overall inference is that, particularly in high-income countries, a significant proportion of attendances in non-epidemic times do not need emergency care, but it is possible some children attended at a later stage of their illness during epidemics/pandemics. There are insufficient data to demonstrate whether this occurs in low-middle income countries as well.

The impact of epidemics on health seeking behaviour when emergency care is required was mixed in our review. Lynn *et al*¹⁰³ found a delayed presentation was a suspected causative factor in nine deaths. Increases in severe diabetic ketoacidosis^{74 75 91 92} and complicated acute appendicitis presentations^{86 144} are examples of this. However, Chong *et al*³⁵ did not observe a large deferred increase in 'priority 1 (most ill)' cases in the early post-lockdown period and Roland *et al*¹⁰⁵ noted a 'low rate of reported delays' at 3.8% (n=51) and, of these, the admission rate was also low at 11.8% (n=6).

This review highlights the need for reflection on the structure of emergency services post-pandemic. Policy makers need to urgently consider how the public can address minor illness and injury at home, or at least more locally, rather than seeking emergency care services as clearly many children were managed without healthcare intervention during pandemics. Our data highlight that public reactions could change according to their perception of risk related to that pandemic (eg, COVID-19 vs H1N1). The increase in visits to the PED during the H1N1 pandemic may then have been a result of the higher mortality and parental fears of adverse outcomes.^{145 137} This suggests policy makers and health authorities may need to provide the public 'personalised and periodically updated communication' as opposed to generic advice and be aware messaging can reassure or scare the public.

The vast majority of the articles included within this review had a retrospective observational methodology which brings with it inherent limitations. Many of the articles analysed the effect at a single hospital/city, which may not allow their data to be generalised, but the large amount of studies from many countries included in this review improve on this limitation. Some studies also had no or very few cases of the epidemic disease at the hospital or in the region, which may have been a cause behind differing changes in PED visits between studies, making comparisons difficult. It is noted that the pandemic still continues and so the final impact on attendances is not certain with further analysis of trends greater than 1–2 years needed. Finally, redeployment of staff did occur during the COVID-19 pandemic but the impact of this was not directly measured in the papers we reviewed. Nor did they take into account other system changes, such as the development or closure of primary care services which also may have had an impact on attendances.

CONCLUSION

We found that PED attendances may increase or decrease during these pandemics and epidemics, the reasons being multifactorial, and ultimately individual experiences and behaviours will influ-

ence parent/patient decision-making during these periods of public health crisis. As public health messaging can impact on public behaviours, governing bodies and public health departments must be aware how fear of viruses among the general public may influence their response to public health advice. We have found inequity in the research on epidemic diseases affecting children's presentations to emergency care and this should be a worldwide health policy focus.

Author affiliations

¹SAPPHIRE Group, Health Sciences, University of Leicester, Leicester, UK

²Paediatric Emergency Medicine Leicester Academic (PEMLA) Group, University Hospitals of Leicester NHS Trust, Leicester, UK

³School of Medicine, University of Leicester, Leicester, UK

⁴Northampton General Hospital NHS Trust, Northampton, UK

⁵Department of Paediatric Emergency Medicine, St. Mary's Hospital - Imperial College NHS Healthcare Trust, London, UK

⁶Division of Emergency Medicine, University College London NHS Foundation Trust, London, UK

⁷Division of Pediatric Emergency Medicine, Università degli Studi di Padova, Padova, Italy

⁸Health Informatics Team, Division of Clinical Studies, Institute of Cancer Research, London, UK

⁹Department of Women, Child and Public Health, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Lazio, Italy

¹⁰Università Cattolica del Sacro Cuore, Rome, Italy

¹¹Imperial College Medical School, Imperial College London, London, UK

¹²Department of Child and Adolescent Health, Mater Dei Hospital, Msida, Malta

¹³Emergency Department & Trauma Center, Ospedale Paediatrico Meyer Firenze, Florence, Italy

¹⁴Department of General Paediatrics, Erasmus Universiteit Rotterdam, Rotterdam, The Netherlands

¹⁵Department of Paediatric Emergency Medicine, Heim Pal National Paediatric Institute, Budapest, Hungary

¹⁶Paediatric Emergency Department, Hôpital Universitaire Robert-Debre, Paris, France

¹⁷Section of Paediatric Infectious Diseases, Imperial College London, London, UK

Twitter Damian Roland @damian_roland and Ruud Gerard Gerard Nijman @rgnijnman

Contributors Damian Roland (DR) and AG designed the study with all authors contributing to the development PROSPERO protocol. DR, AG & D Razzaq were responsible for initial abstract identification and data extraction. DR is guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Map disclaimer The inclusion of any map (including the depiction of any boundaries therein), or of any geographic or locational reference, does not imply the expression of any opinion whatsoever on the part of BMJ concerning the legal status of any country, territory, jurisdiction or area or of its authorities. Any such expression remains solely that of the relevant source and is not endorsed by BMJ. Maps are provided without any warranty of any kind, either express or implied.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material This content has been supplied by the author(s). It has not been vetted

by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

This article is made freely available for personal use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iDs

Damian Roland <http://orcid.org/0000-0001-9334-5144>

Katy Rose <http://orcid.org/0000-0002-2020-4161>

Danilo Buonsenso <http://orcid.org/0000-0001-8567-2639>

Rianne oostenbrink <http://orcid.org/0000-0001-7919-8934>

Ian K Maconochie <http://orcid.org/0000-0001-6319-8550>

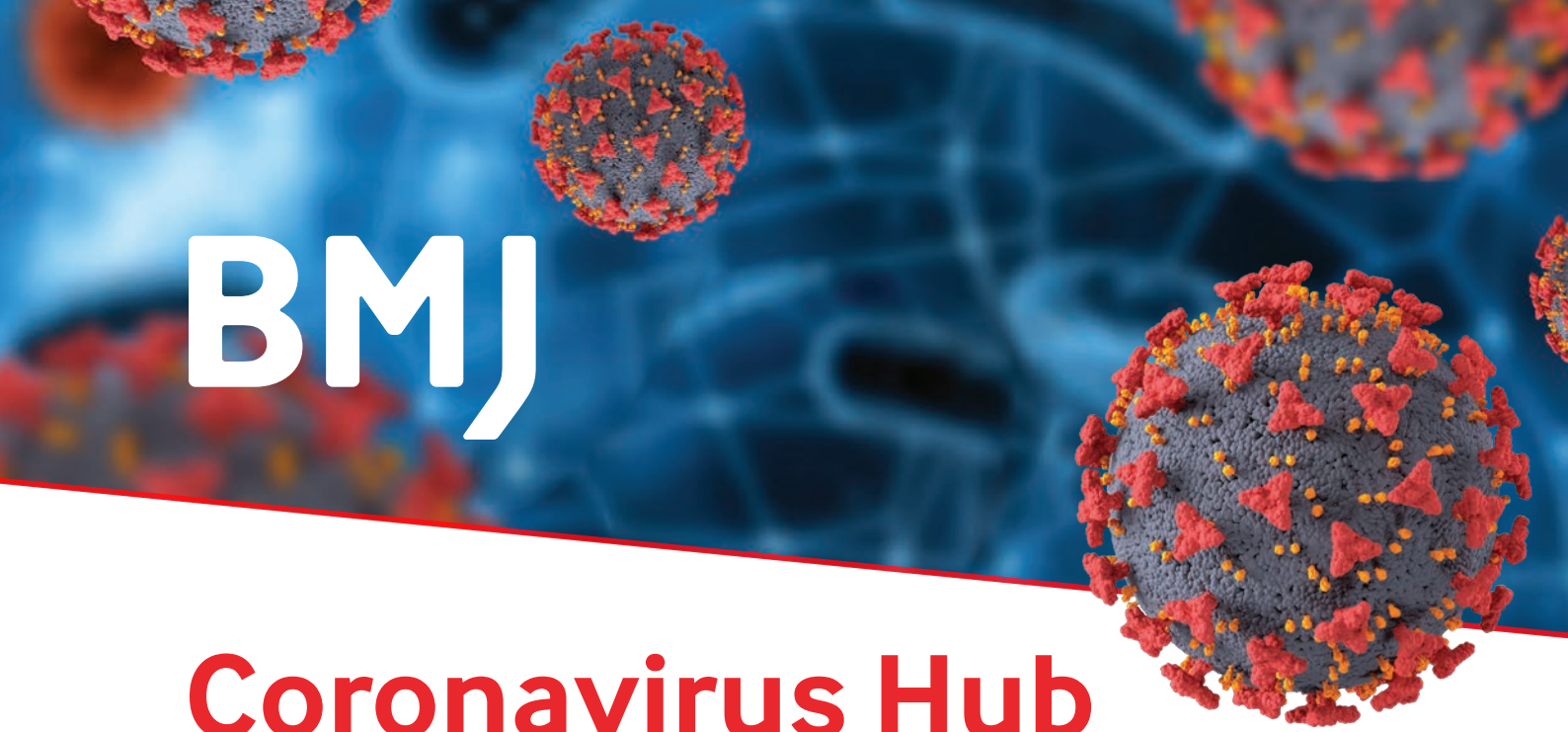
Henriette A Moll <http://orcid.org/0000-0001-9304-3322>

Ruud Gerard Gerard Nijman <http://orcid.org/0000-0001-9671-8161>

REFERENCES

- Hartnett KP, Kite-Powell A, DeVies J, et al. Impact of the COVID-19 Pandemic on Emergency Department Visits - United States, January 1, 2019-May 30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:699-704.
- Hoang A, Chorath K, Moreira A, et al. COVID-19 in 7780 pediatric patients: a systematic review. *EClinicalMedicine* 2020;24:100433.
- Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ* 2020;370:m3249.
- Lazzerini M, Barbi E, Apicella A, et al. Delayed access or provision of care in Italy resulting from fear of COVID-19. *Lancet Child Adolesc Health* 2020;4:e10-11.
- Wilder-Smith A, Osman S. Public health emergencies of international concern: a historic overview. *J Travel Med* 2020;27. doi:10.1093/jtm/taaa227. [Epub ahead of print: 23 12 2020].
- World Health Organization. *International health regulations (2005)*. 3rd edn. Geneva, Switzerland: World Health Organization, 2016.
- Nijman RG, Honeyford K, Farrugia R, et al. Presentations of children to emergency departments across Europe and the COVID-19 pandemic: a multinational observational study. *PLoS Med* 2022;19:e1003974.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
- Study Quality Assessment Tools [Internet]. 2021. Available: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>
- Morello F, Bima P, Ferreri E, et al. After the first wave and beyond lockdown: long-lasting changes in emergency department visit number, characteristics, diagnoses, and hospital admissions. *Intern Emerg Med* 2021;16:1683-90.
- Nicastro E, Mazza A, Gervasoni A, et al. A pediatric emergency department protocol to avoid intrahospital spread of SARS-CoV-2 during the outbreak in Bergamo, Italy. *J Pediatr* 2020;222:331-5.
- Clavenna A, Nardelli S, Sala D, et al. Impact of COVID-19 on the pattern of access to a pediatric emergency department in the Lombardy region, Italy. *Pediatr Emerg Care* 2020;36:e597-8.
- Lázaro Carreño MJ, Barris Fernández A, Quintero García D, et al. Paediatric emergencies during the COVID-19 pandemic. *Glob Pediatr Health* 2021;8:2333794X21989528.
- Honeyford K, Goughan C, Nijman R. Changes in emergency department attendances before and after COVID-19 lockdown implementation: a cross sectional study of one urban NHS Hospital trust. *medRxiv* 2020:2020.07.20.20157560.
- Manzoni P, Militello MA, Fiorica L, et al. Impact of COVID-19 epidemics in paediatric morbidity and utilisation of hospital paediatric services in Italy. *Acta Paediatr* 2021;110:1369-70.
- Cella A, Marchetti F, Iughetti L, et al. Italian COVID-19 epidemic: effects on paediatric emergency attendance - a survey in the Emilia Romagna region. *BMJ Paediatr Open* 2020;4:e000742.
- Santi L, Golinelli D, Tampieri A, et al. Non-COVID-19 patients in times of pandemic: emergency department visits, hospitalizations and cause-specific mortality in northern Italy. *PLoS One* 2021;16:e0248995.
- Bover-Bauza C, Rosselló Gomila MA, Diaz Pérez D, et al. The impact of the SARS-CoV-2 pandemic on the emergency department and management of the pediatric asthmatic patient. *J Asthma Allergy* 2021;14:101-8.

19. Ferrero F, Ossorio ME, Torres FA, et al. Impact of the COVID-19 pandemic in the paediatric emergency department attendances in Argentina. *Arch Dis Child* 2021;106:e5.
20. Vierucci B, Bacci C, Mucaria C, et al. How COVID-19 pandemic changed children and adolescents use of the emergency department: the experience of a secondary care pediatric unit in central Italy. *SN Compr Clin Med* 2020;2:1-11.
21. Matera L, Nenna R, Rizzo V, et al. SARS-CoV-2 pandemic impact on pediatric emergency rooms: a multicenter study. *Int J Environ Res Public Health* 2020;17:8753.
22. Lin C-F, Huang Y-H, Cheng C-Y, et al. Public health interventions for the COVID-19 pandemic reduce respiratory tract infection-related visits at pediatric emergency departments in Taiwan. *Front Public Health* 2020;8:604089.
23. Keyes D, Hardin B, Sweeney B, et al. Change in urban and non-urban pattern of ED use during the COVID-19 pandemic in 28 Michigan hospitals: an observational study. *BMJ Open* 2021;11:e043024.
24. Cozzi G, Zanchi C, Giangreco M, et al. The impact of the COVID-19 lockdown in Italy on a paediatric emergency setting. *Acta Paediatr* 2020;109:157-9.
25. Ciacchini B, Tonioli F, Marciano C, et al. Reluctance to seek pediatric care during the COVID-19 pandemic and the risks of delayed diagnosis. *Ital J Pediatr* 2020;46:87.
26. Rotulo GA, Percivali B, Molteni M, et al. The impact of COVID-19 lockdown on infectious diseases epidemiology: the experience of a tertiary Italian pediatric emergency department. *Am J Emerg Med* 2021;43:115-7.
27. Talarico V, Pinto L, Marsaglia GL, et al. Impact of novel coronavirus Disease-19 (COVID-19) pandemic in Italian pediatric emergency departments: a national survey. *Ital J Pediatr* 2021;47:47.
28. Mekouli N, Razine R, Bassat Q, et al. The Effect of COVID-19 on Paediatric Emergencies and Admissions in Morocco: Cannot See the Forest for the Trees? *J Trop Pediatr* 2021;67:fmaa046.
29. Liguoro I, Pilotto C, Vergine M, et al. The impact of COVID-19 on a tertiary care pediatric emergency department. *Eur J Pediatr* 2021;180:1497-504.
30. Iozzi L, Brambilla I, Foidelli T, et al. Paediatric emergency department visits fell by more than 70% during the COVID-19 lockdown in Northern Italy. *Acta Paediatr* 2020;109:2137-8.
31. Davico C, Marcotulli D, Lux C, et al. Where have the children with epilepsy gone? an observational study of seizure-related accesses to emergency department at the time of COVID-19. *Seizure* 2020;83:38-40.
32. Chaiyachati BH, Agawu A, Zor JJ, et al. Trends in pediatric emergency department utilization after institution of coronavirus Disease-19 mandatory social distancing. *J Pediatr* 2020;226:274-7.
33. Angoulvant F, Ouldali N, Yang DD, et al. Coronavirus disease 2019 pandemic: impact caused by school closure and national lockdown on pediatric visits and admissions for viral and nonviral infections—a time series analysis. *Clin Infect Dis* 2021;72:319-22.
34. Valitutti F, Zengeri L, Mauro A, et al. Effect of population Lockdown on pediatric emergency room demands in the era of COVID-19. *Front Pediatr* 2020;8:521.
35. Chong S-L, Soo JSL, Allen JC, et al. Impact of COVID-19 on pediatric emergencies and hospitalizations in Singapore. *BMJ Paediatr* 2020;20:562.
36. Scaramuzza A, Tagliaferri F, Bonetti L, et al. Changing admission patterns in paediatric emergency departments during the COVID-19 pandemic. *Arch Dis Child* 2020;105:704-6.
37. Ciofi Degli Atti ML, Campana A, Muda AO, et al. Facing SARS-CoV-2 pandemic at a COVID-19 regional children's hospital in Italy. *Pediatr Infect Dis J* 2020;39:e221-5.
38. Goldman RD, Grafstein E, Barclay N, et al. Paediatric patients seen in 18 emergency departments during the COVID-19 pandemic. *Emerg Med J* 2020;37:773-7.
39. Sethuraman U, Stankovic C, Singer A, et al. Burn visits to a pediatric burn center during the COVID-19 pandemic and 'Stay at home' period. *Burns* 2021;47:491-2.
40. Levene R, Fein DM, Silver EJ, et al. The ongoing impact of COVID-19 on asthma and pediatric emergency health-seeking behavior in the Bronx, an epicenter. *Am J Emerg Med* 2021;43:109-14.
41. Lavisier BdeM, Barriacanal MB, Lavisier BdeM. Impact of the COVID-19 pandemic on emergency department: early findings from a hospital in Madrid. *Am Pediatr* 2020;93:313-22.
42. Kociejowski A, Hobart C, Jina R, et al. Comparison of presentations to the emergency department during the COVID-19 pandemic (COPED-C). *J Public Health* 2021;43:731-8.
43. Raman R, Madhusudan M. Impact of the COVID-19 pandemic on admissions to the pediatric emergency department in a tertiary care hospital. *Indian J Pediatr* 2021;88:392.
44. Dopfer C, Wetzel M, Zychlinsky Schaffr A, et al. COVID-19 related reduction in pediatric emergency health-care utilization - a concerning trend. *BMC Pediatr* 2020;20:427.
45. Isba R, Edge R, Auerbach M, et al. COVID-19: transatlantic declines in pediatric emergency admissions. *Pediatr Emerg Care* 2020;36:551-3.
46. Claudet I, Marchand-Tonel C, Ricco L, et al. During the COVID-19 quarantine, home has been more harmful than the virus for children? *Pediatr Emerg Care* 2020;36:e538-40.
47. Jang KM, Ahn JY, Choi HJ, et al. Pediatric emergency department utilization and coronavirus disease in Daegu, Korea. *J Korean Med Sci* 2021;36:e11.
48. Walker LE, Heaton HA, Monroe RJ, et al. Impact of the SARS-CoV-2 pandemic on emergency department presentations in an integrated health system. *Mayo Clin Proc* 2020;95:2395-407.
49. Swedo E, Idaiakadar N, Leemis R, et al. Trends in US Emergency Department Visits Related to Suspected or Confirmed Child Abuse and Neglect Among Children and Adolescents Aged <18 Years Before and During the COVID-19 Pandemic - United States, January 2019-September 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1841-7.
50. Westgard BC, Morgan MW, Vazquez-Benitez G, et al. An analysis of changes in emergency department visits after a state declaration during the time of COVID-19. *Ann Emerg Med* 2020;76:595-601.
51. Mann JA, Patel N, Bragg J, et al. Did children stay safe? Evaluation of burns presentations to a children's emergency department during the period of COVID-19 school closures. *Arch Dis Child* 2021;106:e18.
52. Bailhache M, Ong N, Worbe M, et al. Unlike infectious diseases, respiratory disease emergencies rose after compulsory school attendance following the French COVID-19 lockdown. *Acta Paediatr* 2021;110:1295-6.
53. Akaake LM, Hendrikse C, Spittal G, et al. Cross-Sectional study of paediatric care mix presenting to an emergency centre in Cape town, South Africa, during COVID-19. *BMJ Paediatr Open* 2020;4:e000801.
54. Pines JM, Zocchi MS, Black BS, et al. Characterizing pediatric emergency department visits during the COVID-19 pandemic. *Emerg Med J* 2021;41:201-4.
55. Hughes HE, Hughes TC, Morbey R, et al. Emergency department use during COVID-19 as described by syndromic surveillance. *Emerg Med J* 2020;37:600-4.
56. Choi DH, Jung JY, Suh D, et al. Impact of the COVID-19 outbreak on trends in emergency department utilization in children: a multicenter retrospective observational study in Seoul metropolitan area, Korea. *J Korean Med Sci* 2021;36:e44.
57. Lam CN, Axen S, Terp S, et al. Who Stayed home under Safer-at-Home? impacts of COVID-19 on volume and Patient-Mix at an emergency department. *West J Emerg Med* 2021;22:234-43.
58. Cornelli L, Scioscioli F, Cervellini G. Impact of the COVID-19 pandemic on census, organization and activity of a large urban emergency department. *Acta Biomed* 2020;91:45-9.
59. Sokoloff WC, Krief WJ, Giusto KA, et al. Pediatric emergency department utilization during the COVID-19 pandemic in New York City. *Am J Emerg Med* 2021;45:100-4.
60. Even L, Lipshaw MJ, Wilson PM, et al. Pediatric emergency department volumes and throughput during the COVID-19 pandemic. *Am J Emerg Med* 2021;46:739-41.
61. Bothara RK, Raina A, Carne B, et al. Paediatric presentations to Christchurch hospital emergency department during COVID-19 lockdown. *J Paediatr Child Health* 2021;57:877-82.
62. Raucci U, Musolino AM, Di Lallo D, et al. Impact of the COVID-19 pandemic on the emergency department of a tertiary children's hospital. *Ital J Pediatr* 2021;47:21.
63. Kruckevych D, Arrat M, Levanon S, et al. Trends in burn injuries in northern Israel during the COVID-19 lockdown. *J Burn Care Res* 2021;42:135-40.
64. Dann L, Fitzsimons J, Gorman KM, et al. Disappearing act: COVID-19 and paediatric emergency department attendances. *Arch Dis Child* 2020;105:810-1.
65. Williams TC, MacRae C, Swann OV, et al. Indirect effects of the COVID-19 pandemic on paediatric health-care use and severe disease: a retrospective national cohort study. *Arch Dis Child* 2021;106:911-7.
66. Shanmugavadivel D, Liu J-F, Gilhooley C, et al. Changing patterns of emergency paediatric presentations during the first wave of COVID-19: learning for the second wave from a UK tertiary emergency department. *BMJ Paediatr Open* 2021;5:e000967.
67. Masetti R, Corsini I, Leardini D, et al. Presentations to the emergency department in Bologna, Italy, during COVID-19 outbreak. *BMJ Paediatr Open* 2020;4:e000748.
68. Sharma S, Wong D, Schomberg J, et al. COVID-19: differences in sentinel injury and child abuse reporting during a pandemic. *Child Abuse Negl* 2021;116:104990.
69. Haddadin Z, Blozinski A, Fernandez K, et al. Changes in pediatric emergency department visits during the COVID-19 pandemic. *Hosp Pediatr* 2021;11:e57-60.
70. Cheek JA, Craig SS, West A, et al. Emergency department utilisation by vulnerable paediatric populations during the COVID-19 pandemic. *Emerg Med Australas* 2020;32:870-1.
71. DeLaroche AM, Rodean J, Aronson PL, et al. Pediatric Emergency Department Visits at US Children's Hospitals During the COVID-19 Pandemic. *Pediatrics* 2021;147:e2020039628.
72. Ang HHE, Omar E, Pek JH. Decrease in emergency department attendances during COVID-19 especially in school-going children. *Ann Acad Med Singap* 2021;50:184-7.
73. McDonnell T, Nicholson E, Conlon C, et al. Assessing the impact of COVID-19 public health stages on paediatric emergency attendance. *Int J Environ Res Public Health* 2020;17:6719.
74. Jacob R, Weiser G, Krupik D, et al. Diabetic ketoacidosis at emergency department presentation during the first months of the SARS-CoV-2 pandemic in Israel: a multicenter cross-sectional study. *Diabetes Ther* 2021;12:1569-74.
75. Lawrence C, Seckold R, Smart C, et al. Increased paediatric presentations of severe diabetic ketoacidosis in an Australian tertiary centre during the COVID-19 pandemic. *Diabet Med* 2021;38:e14417.
76. Isba R, Edge R, Jenner R, et al. Where have all the children gone? decreases in paediatric emergency department attendances at the start of the COVID-19 pandemic of 2020. *Arch Dis Child* 2020;105:704.
77. Montalva L, Haffreingue A, Ali L, et al. The role of a pediatric tertiary care center in avoiding collateral damage for children with acute appendicitis during the COVID-19 outbreak. *Pediatr Surg Int* 2020;36:1397-405.
78. Wong PL, Antoniou G, Williams N, et al. Disruption of paediatric orthopaedic hospital services due to the COVID-19 pandemic in a region with minimal COVID-19 illness. *J Child Orthop* 2020;14:245-51.
79. Ali S, Khan MA, Rehman IU, et al. Impact of covid 19 pandemic on presentation, treatment and outcome of paediatric surgical emergencies. *J Ayub Med Coll Abbottabad* 2020;32(Suppl 1):S621-4.
80. Sahin E, Akcali O. What has changed in orthopaedic emergency room during covid - 19 pandemic: A single tertiary center experience. *Acta Medica Mediterranea* 2021;37:521.
81. Rougierau G, Guedj R, Irtan S, et al. Emergency department visits for pediatric traumatic injuries during general confinement: a single-center study in an urban setting. *Archives de Pédiatrie* 2021;28:249-51.
82. Bram JT, Johnson MA, Magee LC, et al. Where have all the fractures gone? the epidemiology of pediatric fractures during the COVID-19 pandemic. *J Pediatr Orthop* 2020;40:373-9.
83. Keays G, Friedman D, Gagnon I. Injuries in the time of COVID-19. *Health Promot Chronic Dis Prev Can* 2020;40:336-41.
84. Sherman WF, Khadra HS, Kale NN, et al. How did the number and type of injuries in patients presenting to a regional level 1 trauma center change during the COVID-19 pandemic with a Stay-at-home order? *Clin Orthop Relat Res* 2021;479:266-75.
85. Nelson CP, Kurtz MP, Logvinenko T, et al. Timing and outcomes of testicular torsion during the COVID-19 crisis. *J Pediatr Urol* 2020;16:841.e1-841.e5.
86. Delgado-Miguel C, Muñoz-Serrano AJ, Miguel-Ferrero M, et al. Complicated acute appendicitis during COVID-19 pandemic: the hidden epidemic in children. *Eur J Pediatr Surg* 2022;32:268-73.
87. Gaitero Tristán J, Souto Romero H, Escalada Pelletiero S, et al. Acute appendicitis in children during the COVID-19 pandemic: neither delayed diagnosis nor worse outcomes. *Pediatr Emerg Care* 2021;37:185-90.
88. Lefr KA, Setzer E, Cicero MX, et al. Changes in pediatric emergency department visits for mental health during the COVID-19 pandemic: a cross-sectional study. *Clin Child Psychol Psychiatry* 2021;26:33-8.
89. Joyce LR, Richardson SK, McCombie A, et al. Mental health presentations to Christchurch hospital emergency department during COVID-19 lockdown. *Emerg Med Australas* 2021;33:324-30.
90. Leeb RT, Bitsko RH, Radhakrishnan L, et al. Mental Health-Related Emergency Department Visits Among Children Aged <18 Years During the COVID-19 Pandemic - United States, January 1-October 17, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1675-80.
91. Rabbone I, Schiaffini R, Cherubini V, et al. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? *Diabetes Care* 2020;43:2870-2.
92. Dayal D, Gupta S, Rathitha D, et al. Missing during COVID-19 lockdown: children with onset of type 1 diabetes. *Acta Paediatr* 2020;109:2144-6.
93. Taquehel C, Diwadkar AR, Sayed S, et al. Pediatric asthma health care utilization, viral testing, and air pollution changes during the COVID-19 pandemic. *J Allergy Clin Immunol Pract* 2020;8:3378-87.
94. Kenyon CG, Hill DA, Henrickson SE, et al. Initial effects of the COVID-19 pandemic on pediatric asthma emergency department utilization. *J Allergy Clin Immunol Pract* 2020;8:2774-6.
95. Bai J, Xu T, Ji A-P, et al. Impact of COVID-19 on oral emergency services. *Int Dent J* 2021;71:27-31.
96. Nowlin A, Lai K, Mailis A, et al. Healthcare utilization among children and adolescents with sickle cell disease during the COVID-19 pandemic. *Blood* 2020;136:30-1.
97. Shah K, Camhi SS, Sridhar J, et al. Impact of the coronavirus pandemic on pediatric eye-related emergency department visits. *J Aapos* 2020;24:367-9.
98. Grigoletto V, Cognigni M, Occhipinti AA, et al. Rebound of severe alcoholic intoxications in adolescents and young adults after COVID-19 lockdown. *Journal of Adolescent Health* 2020;67:727-9.
99. Nourazari S, Davis SR, Granovsky R, et al. Decreased hospital admissions through emergency departments during the COVID-19 pandemic. *Am J Emerg Med* 2020;42:203-10.
100. Kuitunen I, Artama M, Mäkelä L, et al. Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. *Pediatr Infect Dis J* 2020;39:e423-7.
101. Dicker B, Swain A, Todd VE, et al. Changes in demand for emergency ambulances during a nationwide lockdown that resulted in elimination of COVID-19: an observational study from New Zealand. *BMJ Open* 2020;10:e044726.
102. Monzani A, Ragazzoni L, Della Corte F, et al. COVID-19 pandemic: perspective from Italian pediatric emergency physicians. *Disaster Med Public Health Prep* 2020;14:648-51.
103. Lynn RM, Avis JL, Lenton S, et al. Delayed access to care and late presentations in children during the COVID-19 pandemic: a snapshot survey of 4075 paediatricians in the UK and Ireland. *Arch Dis Child* 2021;106:e8.
104. Chiu TGA, Leung WCY, Zhang Q, et al. Changes in pediatric seizure-related emergency department attendances during COVID-19 - A territory-wide observational study. *J Formos Med Assoc* 2021;120:1647-51.
105. Roland D, Harwood R, Bishop N, et al. Children's emergency presentations during the COVID-19 pandemic. *Lancet Child Adolesc Health* 2020;4:e32-3.
106. Littman AR, Janssen KM, Tong L, et al. Did COVID-19 affect time to presentation in the setting of pediatric testicular torsion? *Pediatr Emerg Care* 2021;37:123-5.
107. McIntosh A, Bachmann M, Siedner MJ, et al. Effect of COVID-19 lockdown on hospital admissions and mortality in rural KaZulu-Natal, South Africa: interrupted time series analysis. *BMJ Open* 2021;11:e047961.
108. Synorck D, Bettelheim L, Liss H, et al. Impact of the 2015 middle East respiratory syndrome outbreak on emergency department visits. *J Hosp Med* 2021;16:e1.
109. Sano K, Nakamura M, Ninomiya H, et al. Large decrease in paediatric hospitalisations during the COVID-19 outbreak in Japan. *BMJ Paediatr Open* 2021;5:e001013.
110. Kruizinga MD, Peeters D, van Veen M, et al. The impact of lockdown on pediatric ED visits and hospital admissions during the COVID-19 pandemic: a multicenter analysis and review of the literature. *Eur J Pediatr* 2021;180:2271-9.
111. Lucero AD, Lee A, Hyun J, et al. Underutilization of the emergency department during the COVID-19 pandemic. *West J Emerg Med* 2020;21:15-23.
112. Sheridan DC, Cloutier R, Johnson K, et al. Where have all the emergency paediatric mental health patients gone during COVID-19? *Acta Paediatr* 2021;110:598-9.
113. Heiber M, Lou WYW. Effect of the SARS outbreak on visits to a community hospital emergency department. *CJEM* 2006;8:323-8.
114. Huang H-H, Yen DH-T, Kao W-F, et al. Declining emergency department visits and costs during the severe acute respiratory syndrome (SARS) outbreak. *J Formos Med Assoc* 2006;105:31-7.
115. Chen W-K, Cheng Y-C, Chung Y-T, et al. The impact of the SARS outbreak on an urban emergency department in Taiwan. *Med Care* 2005;43:168-72.
116. Boutis K, Stephens D, Lam K, et al. The impact of SARS on a tertiary care pediatric emergency department. *CMAJ* 2004;171:1353-8.
117. Paek SH, Kim DK, Lee JH, et al. The impact of middle East respiratory syndrome outbreak on trends in emergency department utilization patterns. *J Korean Med Sci* 2017;32:1576-80.
118. Lee SY, Khung YH, Lim HK, et al. Impact of the 2015 middle East respiratory syndrome outbreak on emergency care utilization and mortality in South Korea. *Yonsei Med J* 2016;57:796-803.
119. Tan RMR, Ganapathy S, Tyebally A, et al. Paediatric emergency department attendances during COVID-19 and SARS in Singapore. *Ann Acad Med Singap* 2021;50:126-34.
120. Hermans V, Zachariah R, Woldeyohannes D, et al. Offering General pediatric care during the hard times of the 2014 Ebola outbreak: looking back at how many came and how well they fared at a Médecins sans Frontières referral hospital in rural Sierra Leone. *BMC Pediatr* 2017;17:134.
121. Christie CD, Melbourne-Chambers R, Ennevor J. Chikungunya in Jamaica - public health effects and clinical features in children. *West Indian Med J* 2016:65.
122. Heymann A, Chodick G, Reichman B, et al. Influence of school closure on the incidence of viral respiratory diseases among children and on health care utilization. *Pediatr Infect Dis J* 2004;23:675-7.
123. Del Beccaro MA, Brownstein DR, Cummings P, et al. Outbreak of Escherichia coli O157:H7 hemorrhagic colitis and hemolytic uremic syndrome: effect on use of a pediatric emergency department. *Ann Emerg Med* 1995;26:598-603.
124. World Bank Country and Lending Groups [Internet]. Available: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups> [Accessed 11 Jul 2021].
125. Schanzer DL, Schwartz B, Mello MJ. Impact of seasonal and pandemic influenza on emergency department visits, 2003-2010, Ontario, Canada. *Acad Emerg Med* 2013;20:388-97.
126. Waseem M, McInerney JE, Perales O, et al. Impact of operational staging to improve patient throughput in an inner-city emergency department during the novel H1N1 influenza surge: a descriptive study. *Pediatr Emerg Care* 2013;29:342-9.
127. Song X, DeBiasi RJ, Campos JM, et al. Comparison of pandemic and seasonal influenza A infections in pediatric patients: were they different? *Influenza Other Respir Viruses* 2012;6:25-7.
128. Graham J, Shirm S, Storm E, et al. Challenges and solutions: pandemic 2009 H1N1 influenza A in a pediatric emergency department. *Am J Disaster Med* 2011;6:211-8.
129. Scarfone RJ, Coffin S, Fieldston ES, et al. Hospital-Based pandemic influenza preparedness and response: strategies to increase surge capacity. *Pediatr Emerg Care* 2011;27:565-72.
130. Arney RL, Armbricht ES, Kennedy BR, et al. Pandemic influenza extension areas in an urban pediatric hospital. *Prehosp Disaster Med* 2012;27:75-80.
131. Sills MR, Hall M, Simon HK, et al. Resource burden at children's hospitals experiencing surge volumes during the spring 2009 H1N1 influenza pandemic. *Acad Emerg Med* 2011;18:158-66.
132. Costello BE, Simon HK, Massey R, Simon MD, Harold K, et al. Pandemic H1N1 influenza in the pediatric emergency department: a comparison with previous seasonal influenza outbreaks. *Ann Emerg Med* 2010;56:643-8.
133. Blumental S, Huisman E, Cornet M-C, et al. Pandemic A/H1N1v influenza 2009 in hospitalized children: a multicenter Belgian survey. *BMC Infect Dis* 2011;11:313.
134. Jales A, Grijalva CG, Zhu Y, et al. Age-Specific Influenza-Related emergency department visits and hospitalizations in 2010-2011 compared with the pandemic year 2009-2010. *Infectious Diseases in Clinical Practice* 2014;22:271-8.
135. McDonnell WM, Nelson DS, Schunk JE. Should we fear 'flu fear' itself? Effects of H1N1 influenza fear on ED use. *Am J Emerg Med* 2012;30:275-82.
136. Trivellin V, Gandini V, Nespoli L. Low adherence to influenza vaccination campaigns: is the H1N1 virus pandemic to be blamed? *Ital J Pediatr* 2011;37:54.
137. Miralby V, Baird JS, Zackai S, et al. Novel influenza A(H1N1) in a pediatric health care facility in New York City during the first wave of the 2009 pandemic. *Arch Pediatr Adolesc Med* 2010;164:24-30.
138. Jales A, Grijalva CG, Zhu Y, et al. Influenza-related hospitalization and ED visits in children less than 5 years: 2000-2011. *Pediatrics* 2015;135:e66-74.
139. Codish S, Novack L, Dreier J, et al. Impact of mass media on public behavior and physicians: an ecological study of the H1N1 influenza pandemic. *Infect Control Hosp Epidemiol* 2014;35:709-16.
140. New South Wales public health network. Progression and impact of the first winter wave of the 2009 pandemic H1N1 influenza in New South Wales, Australia. *Euro Surveill* 2009;14:19365.
141. Fontelo P, Liu F. A review of recent publication trends from top publishing countries. *Syst Rev* 2018;7:147.
142. McHale P, Wood S, Hughes K, et al. Who uses emergency departments inappropriately and when - a national cross-sectional study using a monitoring data system. *BMC Med* 2013;11:258.
143. Riva B, Clavenna A, Cartabia M, et al. Emergency department use by paediatric patients in Lombardy region, Italy: a population study. *BMJ Paediatr Open* 2018;2:e000247.
144. Snapiro O, Rosenberg Danziger C, Krause I, et al. Delayed diagnosis of paediatric appendicitis during the COVID-19 pandemic. *Acta Paediatr* 2020;109:1672-6.
145. Sachedina N, Donaldson LJ. Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. *Lancet* 2010;376:1846-52.



BMJ

Coronavirus Hub

Freely available, all in one place

All covid-19 content from BMJ's 70+ journal portfolio plus Best Practice and BMJ learning too

Why access?

- **Daily updates:** Keep up to date on all aspects of the pandemic
- **Clinical guidance:** Effectively diagnose and manage covid-19
- **Courses:** Refresh your clinical knowledge with online CPD courses
- **Research:** Access the latest covid-related articles from The BMJ and all other BMJ Journals



Visit today:
bmj.com/coronavirus



Scan this code using
your phone's camera

ARTIGO ORIGINAL

Desfechos respiratórios e alérgicos entre crianças de 5 anos expostas a pesticidas

Jessica Y Islam,^{1,2} Jane Hoppin,^{1,2} Ana M Mora,^{3,4} Manuel E Soto-Martinez,⁵ Leonel Córdoba Gamboa,³ Jorge Ernesto Peñaloza Castañeda,³ Brian Reich,^{1,6} Christian Lindh,⁷ Berna van Wendel de Joode³

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2021-218068>).

¹Center for Human Health and the Environment, North Carolina State University, Raleigh, North Carolina, USA

²Department of Biological Sciences, North Carolina State University, Raleigh, North Carolina, USA

³Infants' Environmental Health (ISA) Program, Central American Institute for Studies on Toxic Substances (IRET), Universidad Nacional, Heredia, Costa Rica

⁴Center for Environmental Research and Children's Health (CERCH), University of California, Berkeley, California, USA

⁵Respiratory Department, Hospital Nacional de Niños, San Jose, Costa Rica

⁶Department of Biostatistics, North Carolina State University, Raleigh, North Carolina, USA

⁷Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden

Correspondence to

Professor Berna van Wendel de Joode, Universidad Nacional, Heredia 40101, Costa Rica; berendina.vanwendel.dejoode@una.cr

Received 9 August 2021

Accepted 13 December 2021

Published Online First

24 February 2022



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Islam JY, Hoppin J, Mora AM, et al. *Thorax* doi:10.1136/thoraxjnl-2021-218068

RESUMO

Contexto Pouco se sabe sobre os efeitos dos pesticidas sobre os desfechos respiratórios e alérgicos das crianças. Avaliámos as relações das exposições a pesticidas, pré-natal e atual, aos desfechos respiratórios e alérgicos em crianças do Infants' Environmental Health Study na Costa Rica.

Métodos Entre as crianças de 5 anos (n=303), medimos as concentrações de metabolitos urinários corrigidas para gravidade específicas pré-natais e atuais de inseticidas (clorpirifos, piretroides), fungicidas (mancozeb, pirimetanil, tiabendazol) e 2,4D. Recolhemos informações dos cuidadores sobre os desfechos respiratórios [se alguma vez teve diagnóstico médico de asma ou infeções do trato respiratório inferior (ITRI), pieira e tosse durante os últimos 12 meses] e alérgicas (alergias nasais, erupção cutânea com comichão, eczema). Montámos modelos de regressão logística multivariável separados para concentrações de metabolitos elevadas (percentil $\geq 75.^{\circ}$ (P75)) vs. baixas (<P75) com desfechos respiratórios e alérgicos. Também aplicámos modelos que incluíam concentrações de metabolitos como variáveis de exposição contínua.

Resultados Os desfechos respiratórios nas crianças foram comuns (39% tosse, 20% pieira, 12% asma, 5% ITRI). As elevadas concentrações de metabolitos piretroides atuais (Σ piretroides) foram associadas a pieira (OR=2,37, IC 95%, 1,28 a 4,34), erupção cutânea com comichão (OR=2,747, IC 95%, 1,33 a 5,60), diagnóstico médico de asma e ITRI). A etilenotiourea (ETU) (metabolito específico do mancozeb) está de algum modo associada às ITRI (OR=2,09, IC 95% 0,68 a 6,02). Obtivemos resultados semelhantes ao modelar os Σ piretroides e a ETU como variáveis contínuas. Assistimos a associações inconsistentes ou nulas para a exposição a outros pesticidas e a resultados de saúde.

Conclusões A atual exposição a piretroides pode afetar a saúde respiratória e alérgica da criança aos 5 anos de idade. A atual exposição a mancozeb pode contribuir para ITRI. Estas conclusões são importantes dado que os piretroides são amplamente utilizados em ambientes domésticos e na agricultura e o mancozeb na agricultura.

INTRODUCTION

The possible effects of pesticides on children's respiratory health are a public health concern. Lower respiratory tract infections (LRTI) are leading cause of death among children under 5 years of age, and asthma is the most common chronic disease of childhood, affecting 14% of children globally.¹ Asthma prevalence has been increased during last decades, particularly in low-resource settings.² Respiratory outcomes, including infection and wheezing, during infancy can have long-term consequences for adult respiratory health.³ Only few studies have reported associations of pesticide exposure with adverse respiratory outcomes in young children.^{4,5} Worldwide, exposure to pesticides is common in both agricultural and residential settings, and results

Key messages

What is the key question?

► Are prenatal and current pesticide exposures associated with children's respiratory and allergic outcomes?

What is the bottom line?

► Current, but not prenatal, pesticide exposures were consistently associated with respiratory and allergic outcomes among 5-year-old children, particularly pyrethroid exposures.

Why read on?

► Very little is known about the effects of pesticides on children's respiratory and allergic outcomes, despite their extensive use.

from epidemiological studies of farmworkers have shown that occupational pesticide exposure may affect respiratory health, as it has been associated with increased odds of coughing, wheezing and asthma.⁵⁻⁹

Pesticide exposure assessment in epidemiological studies is challenging, and researchers studying its effects on children's respiratory health have opted for different approaches, including measurement of pesticides, or its metabolites, in personal air samples, blood and urine.¹⁰ The measurement of urinary pesticide metabolites is one of the most-used methods and often considered the gold standard of exposure assessment, because they reflect exposures from all routes, and, generally, concentrations are more easily detected in urine as compared with blood. Nevertheless, as most current-use pesticides have relatively short toxicokinetic half-lives, their urinary metabolites mainly reflect exposures during the last 24 hours and tend to vary substantially for the same person on different days, most likely attenuating exposure-effect associations of chronic health effects.

Several pesticides have been associated with respiratory outcomes in children. Results from a birth cohort in New York City indicated children aged 5–6 years with higher prenatal exposure to piperonyl butoxide (PBO), a synergist for residential pyrethroid insecticides, had more frequent non-infectious cough compared with children with lower exposures.¹¹ On the other hand, the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth cohort showed children with higher prenatal urinary organophosphate (OP) insecticide concentrations in the second half of pregnancy, and higher cumulative OP exposure

Table 1 Demographic characteristics and prevalence of select respiratory outcomes among 303 children from the ISA Population at children's age 5, Matina County, Costa Rica 2015–2016

	N	%
Child's characteristics		
Child's sex		
Female	147	49
Male	156	51
Child current nutritional status		
Underweight or below	3	1
Normal	228	75
Overweight	46	15
Obese	23	8
Missing	3	1
Low birth weight (<2500 grams)		
Yes	9	3
No	289	95
Missing	5	2
Breast feeding duration		
Less than 6 months	76	25
6 months or more	227	75
Current cotinine detected in urine (>1 µg/L)		
Yes	55	18
No	238	79
Missing	10	3
Mother's characteristics		
Parity ≥1	195	64
Maternal smoking during pregnancy	15	5
Cotinine detected in urine during pregnancy (>1 µg/L)	45	15
Maternal smoking history		
Never	278	92
Past	15	5
Current	10	3
Current cotinine detected in urine (maternal)	45	15
Maternal history of asthma	70	23
Current work in agriculture		
Yes	49*	14
No	250	83
Missing	10	3
Partner currently works in agriculture		
Yes	154	51
No	139	46
Missing	10	3
Household characteristics		
Current smoking inside house	32	11
Income per capita at enrolment		
Above poverty line	102	34
Poverty	112	37
Extreme poverty	88	29
Missing	1	0
Food security†		
Low	194	64
Marginal	69	23

Continued

Table 1 Continued

	N	%
High	30	10
Missing	10	3
Daily exposure to smoke of waste burning	50	17
Vector control by ministry of health during last 12 months	169	56
Pesticide use inside home during last 12 months	152	50
Residential distance to banana plantation (metres)		
<50	56	19
50–500	170	56
≥500	77	25

*46 out of 49 mothers currently worked on banana plantations.

†138 out of 154 partners currently worked on banana plantations.

‡Defined using the U.S. Department of Agriculture Food Security Scale.

ISA, Infants' Environmental Health Study.

during childhood had more respiratory symptoms at ages 5 and 7 years.¹² Results from the same cohort indicated cumulative urinary OP-metabolite concentrations between 0.5 and 5 years were associated with decreased lung function at 7 years of age.¹³ In contrast, a cross-sectional study using data from the US National Health and Nutrition Examination Survey in children aged 6–15 years found null associations of urinary OP-metabolite concentrations with current wheeze.¹⁴ Regarding the fungicide mancozeb and its metabolite ethylene thiourea (ETU), results from a small (n=66) cross-sectional study performed in France indicated children with higher urinary ETU had higher prevalence of asthma and rhinitis symptoms at ages 3–10 years.¹⁵ In Costa Rica, results from the Infants' Environmental Health Study (ISA)¹⁶ showed prenatal exposure to the fungicide mancozeb and ETU during the first, but not second, half of pregnancy, was associated with an increased prevalence of LRTI during the first year of life.¹⁷

Several studies^{16–18} have shown women and children from rural areas in the Costa Rica Caribbean are environmentally exposed to various pesticides used in agriculture, including the fungicides mancozeb, pyrimethanil and thiabendazole, the OP-insecticide chlorpyrifos and the herbicide 2,4-D used in pasture for broad leaved weed control as well as pyrethroid-insecticides used for vector control.^{16–17–19–20} On large-scale banana plantations, the predominant crops in our study area, mancozeb is generally applied with light aircrafts on a weekly basis to prevent Sigatoka disease, and about 12 other fungicides are being applied by aerial spraying, while the fungicide thiabendazole is being applied postharvest, before packing the fruits for shipment. In addition, bags treated with insecticides, such as chlorpyrifos, are being used, and highly toxic nematocides are being applied 3–4 times a year.²¹ Regarding vector-control, pyrethroid-insecticides like cypermethrin are used by the Ministry of Health when there is an outbreak of Dengue, chikungunya and Zika fever, and synthetic pyrethroids are commonly used by families at home. Here, we evaluated the association of prenatal and current exposure to chlorpyrifos, pyrethroids, mancozeb, pyrimethanil, thiabendazole and 2,4-D with respiratory and allergic outcomes among 5-year-old children from the ISA study.

METHODS

Study population

As described previously,¹⁶ pregnant women were enrolled from March 2010 to June 2011, if aged ≥15 years, <33 weeks of gestation and living within 5 km of banana plantations in Matina County Costa Rica.^{16–17} Of the 451 women enrolled in the study, 22 (5%) had a miscarriage, stillbirth or neonatal/infant death; and 126 (28%) were lost to follow-up before the 5-year study visit in 2015–2016. Mother–child pairs included in this analysis (n=303, 67% attainment since enrolment) were similar in sociodemographic attributes to the initial cohort (n=451) and 293 children provided a urine sample at the 5-year visit.

Table 2 Prevalence of respiratory and allergic outcomes among 303 children from the ISA Population at age 5, Matina County, Costa Rica 2015–2016

Type of outcome	Outcome	N	%
Respiratory	Ever wheeze (symptom of asthma)	97	32
	Current* wheeze (symptom of asthma) †	62	20
	Current symptoms of severe asthma‡	33	11
	Ever doctor-diagnosed asthma†	37	12
	Current dry cough†	118	39
	Ever LRTI	49	16
Allergic	Current LRTI†	15	5
	Ever nasal allergies (allergic rhinitis)	67	22
	Current nasal allergies (allergic rhinitis) †	63	21
	Current allergic rhinoconjunctivitis	42	14
	Ever itchy rash (symptom of eczema)	52	17
	Current itchy rash (symptom of eczema) †	39	13
	Ever doctor-diagnosed eczema†	21	7
	Current medication for eczema	8	3

*Past 12 months.

†Selected for epidemiological analysis.

‡≥4 attacks of wheeze, or >1 night per week sleep disturbance from wheeze, or wheeze affecting speech in the past 12 months.

ISA, Infants' Environmental Health Study; LRTI, lower respiratory tract infection.

Data collection

Data collection of the prenatal and early life visits has been described in detail previously.^{16,17} In this study, we included data from prenatal and 5-year visits. We collected information on sociodemographic and socioeconomic, medical, occupational and environmental variables at each visit (table 1) with a structured questionnaire. We also measured Euclidean distances from residence to the nearest border of closest banana plantation.¹⁶ In addition, at each visit, we collected maternal spot urine samples 1–3 times during pregnancy in 100 mL beakers (Vacuette, sterile), aliquoted them into 15 mL tubes (PerformR Centrifuge tubes, Labcon, sterile) and then stored them at –20°C until shipment to the Division of Occupational and Environmental Medicine at Lund University, Sweden, for analysis.¹⁶

When the children were 5 years old, we visited their homes again and administered their caretakers, mostly mothers (n=291, 96%), a structured questionnaire to collect data on their child's health. Information on respiratory and allergic outcomes was collected using the International Study of Allergy and Asthma in Children (ISAAC) questionnaire (in Spanish, previously used in Costa Rica).¹⁶ Images or videos for each condition (eg, wheeze, eczema) were provided when applicable. All data were collected using electronic tablets. Children provided a spot urine sample on the day of visit, with help from their caretaker following the same procedures as described before.^{16,17} Anthropometric measurements, including height, weight and waist circumference, were also taken, as described previously.¹⁷

Exposure assessment

Urine samples were analysed for urinary pesticide metabolites using a liquid chromatography mass spectrometer (LC-MS/MS; UFLCRX; Shimadzu Corporation) with a triple quadrupole linear ion trap (QTRAP 5500; AB Sciex) and corrected for specific gravity as described previously.^{16,17,22} We analysed ETU (limit of detection (LOD)=0.08 µg/L) for mancozeb; hydroxypyrimethanil (OHP) (LOD=0.06 µg/L) for pyrimethanil; 5-hydroxythiabendazole (OHT) (LOD=0.03 µg/L) for thiabendazole; 3,5,6-trichloro-2-pyridinol (TCP) (LOD=0.05 µg/L) for chlorpyrifos and 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DCCA) (LOD=0.04 µg/L) for the pyrethroids permethrin, cypermethrin and cyfluthrin; and 3-phenoxybenzoic acid (3-PBA) (LOD=0.03 µg/L) for permethrin, cypermethrin, cyfluthrin, deltamethrin, allethrin, resmethrin and fenvalerate. The herbicide 2,4-D was also measured (LOD=0.02 µg/L). We added the concentrations of 3-PBA and DCCA to create a summary measure of pyrethroid exposure

(ΣPyrethroids). The laboratory takes part in the Erlangen interlaboratory programme for TCP and 3-PBA with excellent results (online supplemental material I and II).

We also measured urinary cotinine concentrations (indicator for exposure to cigarette smoke) and urinary 1-hydroxypyrene and hydroxyphenanthrene concentrations. The latter are biomarkers of exposure to polycyclic aromatic hydrocarbons possibly from smoke from wood or waste burning.^{23,24} As our study was situated in a rural area, we did not measure outdoor pollution (particulate matter (PM) 2.5, PM 10 or ozone). Also, as the Caribbean climate is similar all-year round, without well-defined dry or wet seasons, we also did not consider exposure to pollen.

Outcome assessment

We interviewed mothers or caretakers at home about respiratory and allergic outcomes in their children at 5 years of age with a structured questionnaire. Most questions were from the ISAAC-III questionnaire²⁵ previously used in Costa Rica²⁶ (for more information, see online supplemental table S1). We obtained information about symptoms of asthma (ever and current (=during last 12 months) wheeze), ever doctor-confirmed asthma, current dry cough at night, ever and current LRTI, ever and current rhinitis, ever and current symptoms of eczema (itchy rash) and ever doctor-confirmed eczema. Severe symptoms of asthma were defined as ≥4 attacks of wheeze, or >1 night per week sleep disturbance from wheeze or wheeze-affecting speech in the past 12 months.²⁷

Statistical analyses

We calculated descriptive statistics and distributional plots for all variables. We then estimated bivariate associations between biomarkers of exposure, selected outcomes and covariates using χ^2 tests. We estimated correlations between prenatal and current gravity-corrected urinary pesticide metabolite concentrations using Spearman's correlation coefficients. In our main analyses, we examined associations of prenatal and children's current urinary pesticide metabolite concentrations (modelled as dichotomous variables: highest quartile (≥75th percentile (P75)) vs lowest three quartiles (<P75) as we expected effects at relatively high exposures) with selected respiratory and allergic outcomes using multivariable logistic regression models. We also ran our models with pesticide exposures modelled as continuous variables (ie, log10-transformed specific gravity-corrected urinary pesticide metabolite concentrations). Additionally, we ran our logistic regression models with exposure variables obtained via interviews: current maternal and paternal work in agriculture, pesticide use inside or outside home during last 12 months, governmental spraying for vector control during last 12 months and reported exposure to smoke from waste burning (daily or weekly vs less than weekly). We adjusted our multivariable models *a priori* for maternal smoking during pregnancy (yes/no) and child sex as these have been identified as risk factors for respiratory and allergic diseases in the literature.²⁶ We imputed missing values for covariates (all <5% missing) using data from the nearest available study visit.

We ran several sensitivity analyses to evaluate the robustness of our results. First, we ran models that included both prenatal and current exposures in the same model, while adjusting for child sex and maternal smoking during pregnancy. Second, we added additional variables, reported among at least 5% of the children, described in the literature as possible risk or protective factors for respiratory and allergic diseases^{26,28} that associated (OR >1.5) with one or more of the outcomes and ran models adjusted for: (1) maternal smoking during pregnancy, child sex, parity (0 vs ≥1), breastfeeding (>6 vs ≤6 months); (2) maternal smoking during pregnancy, child sex, parity and maternal history of asthma (yes/no) and (3) models adjusted for current smoking inside house (yes/no), child sex and parity.

Based on the exploratory nature of this analysis, we did not adjust for multiple comparisons. Furthermore, we looked for patterns shown by results, instead of focusing on statistical significance (ie, $p < 0.05$). All statistical analyses were conducted in R (V.3.6.1).

Table 3 Prenatal and current specific-gravity adjusted urinary pesticide metabolite concentrations for children from the ISA study at age 5, Matina County, Costa Rica, 2015–2016

Urinary biomarkers of exposure (µg/L)	Minimum	Percentile					Maximum
		10th	25th	50th	75th	90th	
Averaged prenatal concentrations (n=303)†							
TCP	0.41	0.92	1.31	1.75	2.52	4.19	62.96
ETU	1.03	1.87	2.34	3.32	4.66	6.16	127.38
OHP	<LOD	0.12	0.21	0.56	1.29	3.28	368.55
OHT	<LOD	<LOD	0.03	0.10	0.53	2.35	339.00
2,4-D	0.09	0.17	0.23	0.32	0.54	1.10	79.76
3-PBA	0.10	0.30	0.51	0.83	1.35	2.46	16.96
DCCA	0.15	0.50	0.79	1.32	2.39	3.78	23.56
Σ Pyrethroid*	0.46	0.87	1.28	2.26	3.84	5.95	40.52
Current child's concentrations (n=293)§							
TCP	0.29	0.69	0.98	1.51	2.31	4.04	30.85
ETU	<LOD	0.61	1.16	2.21	3.65	6.82	66.59
OHP	<LOD	0.10	0.23	0.52	1.27	3.39	445.67
OHT	<LOD	<LOD	<LOD	0.07	0.22	1.01	20.26
2,4-D	0.04	0.19	0.24	0.38	0.71	1.49	146.85
3-PBA	0.15	0.52	0.98	2.09	3.78	6.93	35.92
DCCA	0.19	0.83	1.39	2.53	4.52	8.83	44.19
Σ Pyrethroid*	0.41	1.70	2.62	4.60	8.65	14.74	80.12

*Σ Pyrethroid: sum of 3-PBA and DCCA.

[†]TCP, ETU, 3-PBA, DCCA, and 2,4-D=100% > limit of detection (LOD), OHP=96%, OHT=80% > LOD.[‡]Prenatal intra-class correlation coefficient (ICC): TCP=0.41, ETU=0.14, OHP=0.27, OHT=0.39, 2,4-D=0.28, 3-PBA=0.29, and DCCA=0.28.[§]TCP, 3-PBA, DCCA, and 2,4-D=100% > LOD, ETU=99%, OHP=92%, OHT=68% > LOD.

2,4-D, 2,4-Dichlorophenoxyacetic acid; DCCA, 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid; ETU, ethylenethiourea; ISA, Infants' Environmental Health Study; LOD, limit of detection; OHP, Hydroxypyrimethanil; OHT, 5-hydroxythiabendazole; 3-PBA, 3-phenoxybenzoic acid; TCP, 3,5,6 trichloro-2-pyridinol.

RESULTS

A total of 303 children were included in the analysis of prenatal exposures and 293 in the analysis of current exposures. Table 1 shows about half of the children were girls, 75% had a normal nutritional status, almost all (97%) weighed >2500 g at birth, and 75% were breastfed for 6 months or more. Only 5% of mothers smoked during pregnancy. About one-third of households had an income per capita above the poverty line, but 64% experienced low food security. Prevalence of children with ever doctor-confirmed asthma was 12%, while 20% reported current symptoms of asthma (wheeze), 39% dry cough at night and 5% LRTI during the last 12 months (table 2). Fourteen per cent (n=41) of the children had symptoms of severe asthma. Twenty per cent of children had current rhinitis (nasal allergies), 13% had current symptoms of eczema (itchy rash) and 7% had ever doctor-diagnosed eczema. Current wheeze and ever doctor-diagnosed asthma moderately correlated ($r=0.49$), while other outcomes weakly correlated (wheeze and cough: $r=0.31$, cough and nasal allergies: $r=0.35$, others $r\leq 0.2$) (online supplemental table S1).

The pesticide metabolites presented in table 3 were frequently detected in both prenatal ($\geq 80\%$) and current urine samples ($\geq 68\%$). Averaged prenatal and current pesticide metabolite concentrations were not correlated ($r_s=0-0.25$; online supplemental table S2). Prenatal urinary pesticide concentrations generally were highest for ETU (P75=4.66 µg/L), followed by ΣPyrethroids (P75=3.84 µg/L) and 3,5,6 trichloro-2-pyridinol (TCP) (P75=2.52 µg/L). At 5 years, concentrations were usually highest for ΣPyrethroids (P75=8.65 µg/L), followed by DCCA (4.52 µg/L), 3-PBA (P75=3.78 µg/L) and ETU (P75=3.65 µg/L). Prenatal pesticide metabolite concentrations varied more within than between children as intraclass correlation coefficients ranged from 0.14 to 0.41 (table 3).

Predominantly pyrethroid exposures were associated respiratory outcomes. Prenatal DCCA and ΣPyrethroid showed an inverse association with asthma (OR=0.21, 95% CI: 0.05 to 0.61 and OR=0.39, 95% CI 0.13, 0.98, respectively), but not with other respiratory outcomes. In contrast, children with high current pyrethroid exposures had increased odds of current asthma, ever doctor-diagnosed asthma, current LRTI and, to a lesser extent, current cough (table 4, figure 1). We observed the most precise association for high ΣPyrethroid and wheeze: OR=2.37, 95% CI

1.28 to 4.34). Furthermore, children with high current TCP, ETU, OHP and OHT had increased odds (>2.03) of current LRTI, but these estimates were imprecise, as 95% CI ranged from 0.66 to 6.07 (table 4). When we included exposures as $\log_{10}$ -transformed specific gravity-corrected urinary pesticide metabolite concentrations (online supplemental table S3), our findings generally were similar for pyrethroid exposure, for example, for each tenfold increase in ΣPyrethroid, we found increased odds for wheeze (OR=1.99, 95% CI: 0.98 to 4.07), asthma (OR=2.30, 95% CI: 0.96 to 5.57), and current LRTI (OR=3.74, 95% CI: 1.06 to 13.46). Yet, for the other pesticide metabolites the increased odds of LRTI were attenuated, except for ETU (OR: 2.70, 95% CI 0.72, 10.64 for each tenfold increase in ETU). The results of our sensitivity analyses for respiratory outcomes were similar to these presented above (online supplemental tables S4–S8).

We observed mostly null associations of prenatal pesticide exposures with allergic outcomes (table 5), except for high urinary TCP concentrations that were associated with decreased odds of rhinitis (OR=0.49, 95% CI 0.22 to 0.98), and high urinary OHP concentrations that were associated with increased odds of ever doctor-diagnosed eczema (OR=2.39, 95% CI 0.94 to 5.90). Yet, when modelling these exposures as continuous variables, associations were attenuated for prenatal TCP and current nasal allergies (OR=0.63, 95% CI 0.22 to 0.66) as well as prenatal OHP and ever eczema (OR=1.19, 95% CI 0.59 to 2.25) (online supplemental table S9). In addition, high current pyrethroid exposure was associated with current itchy rash (ie, ΣPyrethroid OR=2.74, 95% CI 1.33 to 5.60), but not with current nasal allergies, or ever eczema (figure 1, table 4). The latter association remained when we modelled current pyrethroid exposure as a continuous variable (OR per 10-fold increase in ΣPyrethroid concentrations: 2.90 (95% CI 1.24 to 6.92) (online supplemental table S9). The sensitivity analyses we ran for models of allergic symptoms showed similar findings as presented above (online supplemental tables S10–S14).

A total of 56% of participants reported governmental pesticide spraying at their homes for vector control during the last 12 months, which includes manually application of pyrethroid insecticides with motorised equipment (table 1). Vector control was associated with children's current cough (OR=1.77, 95% CI: 1.08 to 2.91), and current LRTI (OR=2.78, 95% CI 0.84 to 12.53) (online supplemental table S15). Other environmental or occupational

Table 4 ORs, adjusted for maternal smoking during pregnancy and child's sex, of high ($\geq P75$) specific pesticide exposures and childhood respiratory outcomes during last 12 months

	Current wheeze (N=62)		Ever doctor-diagnosed asthma (N=37)		Current dry cough (N=118)		Current LRTI (N=15)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Prenatal metabolites* (n=303)								
TCP	1.52	0.81 to 2.79	0.88	0.37 to 1.92	1.11	0.65 to 1.89	1.09	0.29 to 3.31
ETU	1.22	0.63 to 2.28	0.86	0.35 to 1.9	0.91	0.52 to 1.55	1.11	0.3 to 3.39
OHP	0.58	0.27 to 1.15	0.79	0.32 to 1.77	1.04	0.6 to 1.77	0.74	0.17 to 2.42
OHT	0.65	0.31 to 1.27	0.65	0.25 to 1.49	1.08	0.63 to 1.83	0.43	0.07 to 1.61
2,4-D	1.21	0.63 to 2.25	0.46	0.16 to 1.11	0.86	0.5 to 1.48	1.5	0.45 to 4.42
3PBA	1.22	0.64 to 2.27	0.6	0.23 to 1.38	1.15	0.67 to 1.96	0.7	0.16 to 2.31
DCCA	0.81	0.4 to 1.55	0.21	0.05 to 0.62	0.74	0.42 to 1.27	1.06	0.29 to 3.23
Σ Pyrethroid†	1.12	0.58 to 2.09	0.39	0.13 to 0.98	0.91	0.52 to 1.55	1.04	0.28 to 3.17
Child metabolites* (n=293)								
TCP	0.94	0.48 to 1.79	1.14	0.5 to 2.46	0.78	0.45 to 1.35	2.05	0.66 to 5.89
ETU	0.58	0.27 to 1.15	0.66	0.25 to 1.53	0.94	0.54 to 1.61	2.09	0.68 to 6.02
OHP	1.21	0.63 to 2.26	1.4	0.62 to 2.97	1.29	0.75 to 2.2	2.1	0.68 to 6.07
OHT	1.17	0.61 to 2.2	1.82	0.84 to 3.8	0.91	0.52 to 1.56	2.03	0.66 to 5.85
2,4-D	0.84	0.42 to 1.61	0.54	0.19 to 1.28	0.76	0.43 to 1.31	1.47	0.45 to 4.32
3PBA	1.72	0.92 to 3.17	1.75	0.81 to 3.66	1.41	0.82 to 2.41	2.7	0.91 to 7.82
DCCA	1.95	1.05 to 3.58	2.09	0.98 to 4.36	1.35	0.79 to 2.31	2.06	0.67 to 5.93
Σ Pyrethroid†	2.37	1.28 to 4.34	2.09	0.98 to 4.36	1.58	0.92 to 2.71	2.78	0.94 to 8.04

ISA study at 5 years of age, Matina County, Costa Rica 2015–2016.

*Variables dichotomised at 75th percentile; reference: below 75th percentile.

† Σ Pyrethroid: sum of PBA and DCCA.

2,4-D, 2,4-dichlorophenoxyacetic acid; ETU, ethylenethiourea; OHP, hydroxypyrimethanil; OHT, 5-hydroxythiabenzodazole; 3-PBA, 3-phenoxybenzoic acid, DCCA: 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid; TCP, 3,5,6 trichloro-2-pyridinol.

exposures like maternal or paternal work in agriculture, pesticide use at home or smoke from environmental waste burning were not associated with children's respiratory outcomes or allergic symptoms (online supplemental tables S15, S16).

DISCUSSION

We found current, but not prenatal, pesticide exposures were consistently associated with respiratory and allergic outcomes among 5-year-old children. Particularly current exposures to pyrethroid insecticides may contribute to children's asthma, LRTI and symptoms of eczema (itchy skin rash) at 5 years of age. Current vector control spraying by government, which includes application of pyrethroids, was associated with cough and LRTI. Furthermore, current mancozeb/ETU exposure was somewhat associated with more frequent LRTI. Unexpectedly, children with increased prenatal pyrethroid exposures had less often ever doctor-diagnosed asthma, and the estimated OR was even smaller after adjusting for maternal asthma. Possibly, mothers with asthma used more frequently pyrethroid insecticides during pregnancy, resulting in increased prenatal exposures to pyrethroids. Yet, these prenatal pyrethroids do not seem to lead to an increased asthma at 5 years of age.

Similar to our findings, a birth cohort in Cincinnati found null associations of prenatal urinary pyrethroid metabolite concentrations with wheeze among children aged 8, but no current exposure levels were reported.²⁹ In contrast to our findings, a cohort in New York City reported higher prenatal permethrin and air concentrations were associated with cough, but not wheeze, in children aged 5 years.³⁰ An analysis among a subset of these children indicated prenatal indoor air PBO (a synergist for pyrethroid insecticides), but not current PBO or permethrin, which was associated with cough at age 5–6 years, but not with asthma or wheeze.¹¹ Furthermore, current permethrin was associated with total IgE levels, but not indoor allergen-specific IgE. The authors hypothesised the effect of permethrin exposure, which may have been driven by sensitisation to outdoor pollen or food allergens, and mentioned that cough may be a result of sensory nerve irritation by pyrethroids.¹¹ With respect to studies among adults exposed to pyrethroids, their findings are consistent with ours. The Agricultural Health Study in USA reported current use of pyrethroids was associated with wheeze in farmers,^{6,31} allergic asthma in farmers³²

and female spouses³³ as well as non-allergic asthma in female spouses.³³ A study among rural women workers in South Africa found pyrethroid exposure was associated with the activation of T-helper cells type 2 cytokines (IL-4, IL-5 and IL-13), these mechanisms may be involved in the development of asthma-related outcomes.³⁴

We previously reported increased urinary ETU (metabolite of mancozeb) during the first half of pregnancy was associated with an increased odds of LRTI during the first year of life.¹⁷ In this study, we observed that higher current ETU was somewhat associated with an increased odds of current LRTI; the estimate was imprecise as only 5% of the children had current LRTI. Still, our results suggest a continued effect of high mancozeb/ETU exposure on children's respiratory health. This is somewhat consistent with results from a cross-sectional study among children aged 3–10 years in France (n=66) in which higher urinary ETU was positively associated with symptoms of asthma and rhinitis.¹⁵ Data from occupational studies have shown dithiocarbamate fungicides like mancozeb may affect respiratory function by modulating the immune system, inducing macrophage activation and enhancing the inflammatory response.^{35–37} Median prenatal and current urinary ETU concentrations in our study were about threefold higher than the study in France,¹⁵ which may be explained by the frequent aerial applications of mancozeb performed in the ISA study area.

With respect to OP pesticides, such as chlorpyrifos, results from the CHAMACOS birth cohort have shown both increased prenatal urinary OP-metabolite concentrations during the second half of pregnancy and higher cumulative OP-exposure during childhood were associated with higher odds of respiratory symptoms at ages 5 and 7¹² and decreased lung function at age 7.¹³ In addition, repeated data of 16 school-aged children (6–16 years) with asthma who lived in a farmworker community in Washington State showed that children with higher urinary OP-metabolite concentrations had elevated leukotrienes, an indicator of asthma exacerbation.³⁸ In our study, we measured urinary TCP, a specific metabolite of chlorpyrifos, instead of general OP-metabolites, and found null associations for prenatal and current TCP with most respiratory or allergic outcomes at age 5 years. Although imprecise, children with high current TCP concentrations had increased odds of LRTI, whereas those with

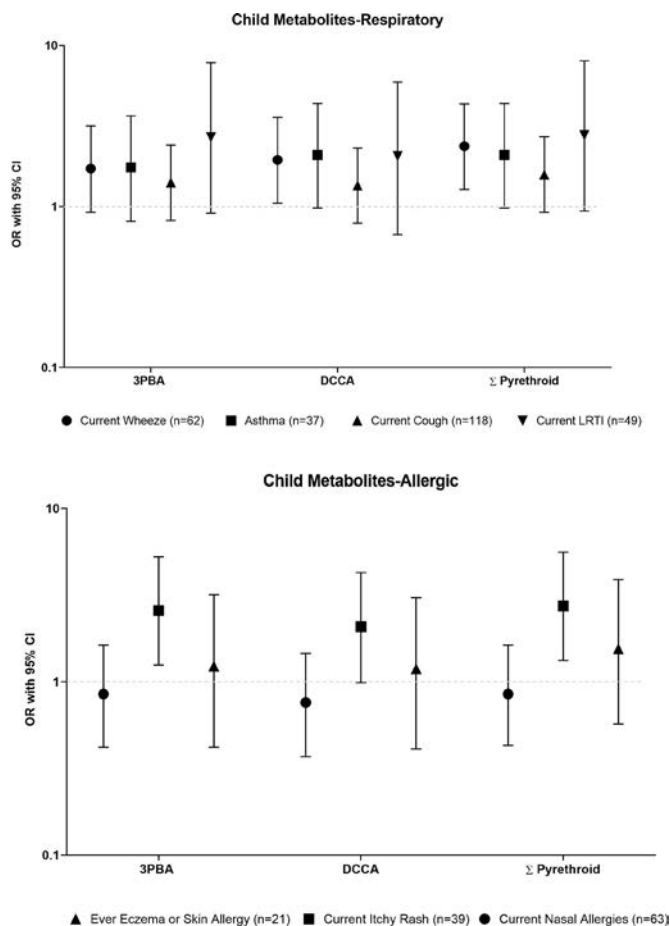


Figure 1 ORs, adjusted for maternal smoking during pregnancy and child's sex, of high ($\geq P75$) Σ pyrethroid exposures and childhood respiratory and allergic outcomes. ISA study at 5 years of age, Matina County, Costa Rica 2015–2016. ORs presented on the logarithmic scale. 3-PBA, 3-phenoxybenzoic acid, DCCA, 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid.

high prenatal TCP concentrations had decreased odds of eczema. Yet, these associations were attenuated when analysing TCP as

a continuous variable. Although research in children is limited, studies in adults have shown associations between exposure to chlorpyrifos and respiratory outcomes. For example, a study of 69 indigenous women in Costa Rica reported increased odds of wheezing among non-smoker women exposed to chlorpyrifos-treated bags.³⁹ Additionally, a cross-sectional study of 496 Dow Chemical Company's (Midland, MI, USA) employees who worked in chlorpyrifos production found increased odds of acute respiratory infections (OR: 1.49; 95% CI 1.8 to 2.5) as compared with unexposed workers (n=911) matched for age, race, sex, pay and year of hire.⁴⁰ Animal and in vitro studies have demonstrated possible mechanisms of chlorpyrifos on respiratory outcomes. In guinea pigs, chlorpyrifos induced airway hyperactivity via neuronal M2 receptor dysfunction, a mechanism involved with asthma.³² Furthermore, an in vitro study observed that chlorpyrifos inhibited the proinflammatory function of macrophages, which may be related to pesticide-induced immunosuppression⁴¹ and contribute to LRTI.

Assessment of pesticide exposure and its effects on human health are difficult. Although biomonitoring of pesticide-specific metabolites is generally considered the gold standard for exposure assessment, metabolites of current-use pesticides mostly reflect exposures during the 24 hours prior to sample collection.¹⁰ Given the intermittent nature of pesticide use, accurately characterising chronic exposures is challenging, which is reflected by the relatively low intraclass correlation coefficients (0.14–0.41) of our repeat prenatal urine samples, and will most likely result in non-specific misclassification of exposure and attenuation of effect estimates. Our study is challenged by its relatively small sample size. We have successfully followed 303 children and their mothers from pregnancy until 5 years of age (67% follow-up), which is a strength. As mother–child pairs included in this analysis were similar in sociodemographic attributes to the initial cohort, selection bias is unlikely. However, since exposure is hard to quantify well and some of the outcomes were rare (ie, LRTI 5%), this study would benefit from a larger sample size with more measurements of pesticide exposure to adequately address the questions related to pesticide exposure and respiratory health.

In our study, we observed a high prevalence of respiratory outcomes measured through the validated and widely used ISAAC questionnaires. In 2012, the global estimated prevalence for symptoms of asthma (defined by self-reported wheezing during last 12

Table 5 ORs adjusted for maternal smoking during pregnancy, child's sex of high ($\geq P75$) specific pesticide exposures and childhood allergic outcomes during last 12 months unless indicated otherwise, ISA study at 5 years of age, Matina County, Costa Rica 2015–2016

	Current nasal allergies (allergic rhinitis) (n=63)		Current itchy rash (atopic eczema) (n=39)		Ever doctor-diagnosed eczema (n=21)	
	OR†	95% CI	OR†	95% CI	OR†	95% CI
Prenatal metabolites* (n=303)						
TCP	0.49	0.22 to 0.98	0.79	0.33 to 1.74	0.68	0.19 to 1.91
ETU	0.74	0.36 to 1.42	0.66	0.26 to 1.51	0.68	0.19 to 1.91
OHP	1.39	0.74 to 2.54	1.03	0.45 to 2.21	2.39	0.94 to 5.9
OHT	0.64	0.31 to 1.25	1.37	0.63 to 2.86	0.94	0.3 to 2.49
2,4-D	1.36	0.72 to 2.51	1.22	0.55 to 2.56	0.95	0.3 to 2.54
3PBA	1.24	0.65 to 2.28	0.53	0.2 to 1.22	1.56	0.57 to 3.93
DCCA	1.01	0.52 to 1.89	1.13	0.5 to 2.38	1.21	0.42 to 3.12
Σ Pyrethroid†	1.01	0.52 to 1.88	0.8	0.33 to 1.76	1.57	0.57 to 3.97
Child metabolites* (n=293)						
TCP	0.96	0.48 to 1.8	0.58	0.22 to 1.33	0.92	0.29 to 2.44
ETU	0.51	0.23 to 1.04	1.37	0.63 to 2.86	0.29	0.05 to 1.05
OHP	1.32	0.69 to 2.44	1.24	0.55 to 2.62	0.68	0.19 to 1.92
OHT	1.19	0.62 to 2.21	1.56	0.73 to 3.24	0.29	0.05 to 1.04
2,4-D	1.19	0.62 to 2.21	1.16	0.52 to 2.45	1.24	0.43 to 3.21
3PBA	0.85	0.42 to 1.63	2.58	1.25 to 5.27	1.23	0.42 to 3.18
DCCA	0.76	0.37 to 1.46	2.08	0.99 to 4.27	1.19	0.41 to 3.06
Σ Pyrethroid†	0.85	0.43 to 1.63	2.74	1.33 to 5.6	1.55	0.57 to 3.89

*Variables dichotomised at 75th percentile; reference: below 75th percentile

† Σ Pyrethroid: sum of PBA and DCCA.

2,4-D, 2,4-dichlorophenoxyacetic acid; ETU, ethylenethiourea; ISA, Infants' Environmental Health Study; OHP, hydroxypyrimethanil; OHT, 5-hydroxythiabendazole; 3-PBA, 3-phenoxybenzoic acid; 3-PBA, 3-phenoxybenzoic acid, DCCA: 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid; TCP, 3,5,6 trichloro-2-pyridinol.

months), rhinitis and symptoms of eczema among children age 6–7 years were 12%, 9% and 8%, respectively.² Compared with these estimates, our population had a higher prevalence of symptoms of asthma (wheezing) (20%), rhinitis (20%) and symptoms of eczema (13%). The 2014 ISAAC Survey in Costa Rica reported a similar prevalence of symptoms of asthma of 24% and eczema (16%), and a higher prevalence of rhinitis (40%) among 6–7-year-old children in Costa Rica.²⁶ Overall, these estimates demonstrate that respiratory and allergic outcomes are an important public health concern for children in Costa Rica.

In conclusion, our study shows that children living in a rural area with large-scale banana farming for export purposes in Costa Rica are exposed to pesticides used in agriculture and vector control, and their exposure levels are relatively high. Given the associations of pesticide exposure with adverse outcomes, interventions to reduce children's pesticide exposure such as elimination of mosquito breeding sites, diversification of monoculture systems, improvement of soil quality, use of non-chemical pest control methods, integrated pest management, revision of application methods and increase in the distance between pesticide applications and residential areas are warranted.

Our findings indicate that current pyrethroid exposure is associated with asthma, wheeze, LRTI and allergic skin rashes. Our results also show that mancozeb exposure may be associated with LRTI. These findings are important as pyrethroids are broadly used worldwide at home and in agriculture, and mancozeb is one of the most-used fungicides in agriculture, possibly putting children's health at risk.

Twitter Berna van Wendel de Joode @bernavanwendel

Acknowledgements We are grateful to the families participating in the ISA study and community partners for sharing their time and information with us. We would also like to thank Michael Cuffney, Juan Camilo Cano, Rosario Quesada, Claudia Hernandez, Diego Hidalgo, Marcela Quirós Lépiz, Alighierie Fajardo Soto, Marie Bengtsson, Daniela Pineda, Moosa Faniband, and Margareta Maxe for their fieldwork, laboratory analyses, and/or data management assistance.

Contributors JYL: analysis and interpretation of data for this paper, drafting the paper. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JH: conception or design of the paper, and the acquisition, analysis, and interpretation of data for this paper, revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Funding acquisition, project administration. AMM: contributions to the conception or design of this paper, revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MES-M: contributions to the conception or design of the work, revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LCG: contributions to the acquisition of data for this study, revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JEP: contributions to the data analysis for this study, revising the paper critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. BR: contributions to the data analysis for this study, revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CL: responsible for the chemical analysis of biomarkers for this study. Revising the paper critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. BVWDJ: conception or design of this paper, and the acquisition, analysis, and interpretation of data for the paper. Drafting parts of this paper and revising it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, funding acquisition, project administration, responsible for the overall content as guarantor.

Funding This publication was made possible by research supported by grant numbers: P01 1 05 296–001 (IDRC); 2010–1211, 2009–2070, and 2014–01095 (Swedish Research Council Formas); R21 ES025374 (NIEHS); and R24 ES028526 (NIEHS).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Scientific Ethics Committee of the Universidad Nacional (CECUNA) registered at IORG with number IRB00006855, approval numbers: CECUNA-11-2009; CECUNA-05-2017. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon request. Deidentified participant data are stored in a secure server by the ISA study team. Please contact the corresponding author for interest in potential data access.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited,

appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Berna van Wendel de Joode <http://orcid.org/0000-0001-9699-5046>

REFERENCES

- 1 Forum of International Respiratory Societies. The global impact of respiratory disease- 2A ED. 2. Sheffield: European Respiratory Society; 2017. ISBN: 9781849840880. https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease.pdf
- 2 Mallol J, Crane J, von Mutius E, et al. The International study of asthma and allergies in childhood (Isaac) phase three: a global synthesis. *Allergol Immunopathol* 2013;41:73–85.
- 3 Rubner FJ, Jackson DJ, Evans MD, et al. Early life rhinovirus wheezing, allergic sensitization, and asthma risk at adolescence. *J Allergy Clin Immunol* 2017;139:501–7.
- 4 Burali RJ, Dultra AF, Ribeiro H. Respiratory and allergic effects in children exposed to Pesticides-A systematic review. *Int J Environ Res Public Health* 2020;17. doi:10.3390/ijerph17082740. [Epub ahead of print: 16 Apr 2020].
- 5 Mamane A, Baldi I, Tessier J-F, et al. Occupational exposure to pesticides and respiratory health. *Eur Respir Rev* 2015;24:306–19.
- 6 Hoppin JA, Umbach DM, Long S, et al. Pesticides are associated with allergic and non-allergic wheeze among male farmers. *Environ Health Perspect* 2017;125:535–43.
- 7 Hoppin JA, Umbach DM, London SJ, et al. Pesticides and adult respiratory outcomes in the agricultural health study. *Ann N Y Acad Sci* 2006;1076:343–54.
- 8 Baldi I, Robert C, Piantoni F, et al. Agricultural exposure and asthma risk in the AGRICAN French cohort. *Int J Hyg Environ Health* 2014;217:435–42.
- 9 Negatu B, Kromhout H, Mekonnen Y, et al. Occupational pesticide exposure and respiratory health: a large-scale cross-sectional study in three commercial farming systems in Ethiopia. *Thorax* 2017;72:498.1–9.
- 10 Fenske RA, Bradman A, Whyatt RM, et al. Lessons learned for the assessment of children's pesticide exposure: critical sampling and analytical issues for future studies. *Environ Health Perspect* 2005;113:1455–62.
- 11 Liu B, Jung KH, Horton MK, et al. Prenatal exposure to pesticide ingredient piperonyl butoxide and childhood cough in an urban cohort. *Environ Int* 2012;48:156–61.
- 12 Raanan R, Harley KG, Balmes JR, et al. Early-Life exposure to organophosphate pesticides and pediatric respiratory symptoms in the CHAMACOS cohort. *Environ Health Perspect* 2015;123:179–85.
- 13 Raanan R, Balmes JR, Harley KG, et al. Decreased lung function in 7-year-old children with early-life organophosphate exposure. *Thorax* 2016;71:148–53.
- 14 Perla ME, Rue T, Cheadle A, et al. Biomarkers of insecticide exposure and asthma in children: a national health and nutrition examination survey (NHANES) 1999–2008 analysis. *Arch Environ Occup Health* 2015;70:309–22.
- 15 Raherison C, Baldi I, Pouquet M, et al. Pesticides exposure by air in vineyard rural area and respiratory health in children: a pilot study. *Environ Res* 2019;169:189–95.
- 16 van Wendel de Joode B, Mora AM, Córdoba L, et al. Aerial application of mancozeb and urinary ethylene thiourea (ETU) concentrations among pregnant women in Costa Rica: the infants' environmental health study (Isa). *Environ Health Perspect* 2014;122:1321–8.
- 17 Mora AM, Hoppin JA, Córdoba L, et al. Prenatal pesticide exposure and respiratory health outcomes in the first year of life: results from the infants' environmental health (Isa) study. *Int J Hyg Environ Health* 2020;225:113474.
- 18 van Wendel de Joode B, Mora AM, Lindh CH, et al. Pesticide exposure and neurodevelopment in children aged 6–9 years from Talamanca, Costa Rica. *Cortex* 2016;85:137–50.
- 19 Córdoba Gamba L, Solano Diaz K, Ruepert C, Córdoba L, Solano K, et al. Passive monitoring techniques to evaluate environmental pesticide exposure: results from the infant's environmental health study (Isa). *Environ Res* 2020;184:109243.
- 20 van Wendel de Joode B, Mora AM, Lindh CH, et al. Pesticide exposure and neurodevelopment in children aged 6–9 years from Talamanca, Costa Rica. *Cortex* 2016;85:137–50.
- 21 Bravo V, Malavassi E de la C, Herrera G. Uso de plaguicidas en cultivos agrícolas como agricultura pesticides use as tool for monitoring health. *Uniciencia* 2013;27:351–76 www.revistas.una.ac.cr/uniciencia
- 22 Norén E, Lindh C, Rylander L, et al. Concentrations and temporal trends in pesticide biomarkers in urine of Swedish adolescents, 2000–2017. *J Expo Sci Environ Epidemiol* 2020;30:756–67.
- 23 Alhadow A, Lindh C, Albin M, et al. Early markers of cardiovascular disease are associated with occupational exposure to polycyclic aromatic hydrocarbons. *Sci Rep* 2017;7:9426.
- 24 Jeng HA, Pan C-H. 1-Hydroxypyrene as a biomarker for environmental health, 2015: 595–612.
- 25 Ellwood P, Asher M, Beasley R. Phase three manual, 2000.
- 26 Soto-Martinez ME, Yock-Corrales A, Camacho-Badilla K, et al. The current prevalence of asthma, allergic rhinitis, and eczema related symptoms in school-aged children in Costa Rica. *J Asthma* 2019;56:360–8.
- 27 Lai CKW, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International study of asthma and allergies in childhood (Isaac). *Thorax* 2009;64:476–83.
- 28 Sherriff A, Peters TJ, Henderson J, et al. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3(1/2) years. *Int J Epidemiol* 2001;30:1473–84.
- 29 Gilden R, Friedmann E, Holmes K, et al. Gestational pesticide exposure and child respiratory health. *Int J Environ Res Public Health* 2020;17:7165.
- 30 Reardon AM, Perzanowski MS, Whyatt RM, et al. Associations between prenatal pesticide exposure and cough, wheeze, and IgE in early childhood. *J Allergy Clin Immunol* 2009;124:852–4.
- 31 Hoppin JA, Umbach DM, London SJ, et al. Chemical predictors of wheeze among farmer pesticide applicators in the agricultural health study. *Am J Respir Crit Care Med* 2002;165:683–9.
- 32 Hoppin JA, Umbach DM, London SJ, et al. Pesticide use and adult-onset asthma among male farmers in the agricultural health study. *Eur Respir J* 2009;34:1296–303.
- 33 Hoppin JA, Umbach DM, London SJ, et al. Pesticides and atopic and nonatopic asthma among farm women in the agricultural health study. *Am J Respir Crit Care Med* 2008;177:11–18.
- 34 Mwanga HH, Dalvie MA, Singh TS, et al. Relationship between pesticide metabolites, cytokine patterns, and asthma-related outcomes in rural women workers. *Int J Environ Res Public Health* 2016;13. doi:10.3390/ijerph13100957. [Epub ahead of print: 27 Sep 2016].
- 35 Weis GCC, Assmann CE, Cadoná FC, et al. Immunomodulatory effect of mancozeb, chlorothalonil, and thiophanate methyl pesticides on macrophage cells. *Ecotoxicol Environ Saf* 2019;182:109420.
- 36 Colosio C, Barcellini W, Maroni M, et al. Immunomodulatory effects of occupational exposure to mancozeb. *Arch Environ Health* 1996;51:445–51.
- 37 Corsini E, Birindelli S, Fustinoni S, et al. Immunomodulatory effects of the fungicide mancozeb in agricultural workers. *Toxicol Appl Pharmacol* 2005;208:178–85.
- 38 Benka-Coker WO, Loftus C, Karr C, et al. Characterizing the joint effects of pesticide exposure and criteria ambient air pollutants on pediatric asthma morbidity in an agricultural community. *Environ Epidemiol* 2019;3:e046.
- 39 Fieten KB, Kromhout H, Heederik D, et al. Pesticide exposure and respiratory health of Indigenous women in Costa Rica. *Am J Epidemiol* 2009;169:1500–6.
- 40 Burns CJ, Cartmill JB, Powers BS, et al. Update of the morbidity experience of employees potentially exposed to chlorpyrifos. *Occup Environ Med* 1998;55:65–70.
- 41 Helali I, Ferchichi S, Maouia A, et al. Modulation of macrophage functionality induced in vitro by chlorpyrifos and carbendazim pesticides. *J Immunotoxicol* 2016;13:745–50.

**PROTEJA
O SEU DOENTE
EM TODAS AS FASES
DA DPOC^{1,2}**

**TRAVA
antes que
seja tarde**

**1 em cada 5 doentes
morre no período de 1 ano*
após a primeira exacerbação com
necessidade de hospitalização.³
Não perca mais tempo.**

*após alta hospitalar



**BEVESPI
AEROSPHERE®**

(glicopirrônio/fumarato de formoterol)
Suspensão Pressurizada para Inalação

DPOC, doença pulmonar obstrutiva crônica

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; abril 2022. Acedido em www.infarmed.pt em outubro 2022. 2. Bevespi Aerosphere 5 microgramas/7,2 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; agosto 2022. Acedido em www.infarmed.pt em outubro 2022. 3. Ho T-W, Tsai Y-J, Ruan S-Y, et al. 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(12):e114866.

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrônio, equivalente a 7,2 microgramas de glicopirrônio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada de 10,4 microgramas de brometo de glicopirrônio, equivalente a 8,3 microgramas de glicopirrônio, 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 crônica (DPOC). **Posologia e modo de administração:** **Posologia:** A dose recomendada é duas inalações duas vezes por dia (duas inalações de manhã e duas inalações à noite). Os doentes devem ser aconselhados a não fazer mais de 2 inalações duas vezes por dia. Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não deve tomar-se uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** 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. **Contra-indicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasmo paradoxal:** Se ocorrer broncospasmo paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Não indicado para utilização em situações agudas:** Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrônio 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 glicose 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. **Compromisso renal:** Como o glicopirrônio 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. **Compromisso hepático:** 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 glicopirrônio 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 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 esteróides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteróides 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_2 -adrenérgicos:** Os bloqueadores β_2 -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β_2 -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β_2 -adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β_2 -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 glicopirrônio 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, Insónia, Tremor, Taquicardia, Palpitações, Arritmias cardíacas (fibrilhação

auricular, taquicardia supraventricular e extra-sístoles), Retenção urinária. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoar> (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 agosto 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 1.0 (agosto 2022).**

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirrónio, equivalente a 7,2 µg de glicopirrónio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirrónio, equivalente a 7,7 µg de glicopirrónio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** **Posologia:** A dose recomendada e máxima é de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** *Idosos:* Não é necessário qualquer ajuste de dose em doentes idosos. *Compromisso renal:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. *Compromisso hepático:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. **População pediátrica:** Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. **Modo de administração:** Para utilização por via inalatória. **Instruções de utilização:** De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus FlowVu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Não indicado para utilização em situações agudas.** Este medicamento não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. **Broncospasma paradoxal:** A administração de formoterol/glicopirrónio/budesonida pode produzir broncospasma paradoxal com sibilos e dispneia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasma 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. fibrilação 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. **Transfusão de terapêutica oral:** Recomenda-se atenção especial nos doentes que fazem a transição de esteróides 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, esteróides e diuréticos. **Hiperglicemia:** A inalação de doses elevadas de agonistas β₂-adrenérgicos pode provocar o aumento da glucose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. **Condições coexistentes:** Este medicamento deve ser utilizado com precaução em doentes com tireotoxicose. **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 farmacodinâmicas:** 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 cobicistate, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos e/ou agonistas β₂-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 β₂-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 cardiosseletivos. **Outras interações farmacodinâmicas:** O tratamento concomitante com quinidina, disipiramida, procainamida, anti-histamínicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procarbazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** **Frequentes:** Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insónia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infecção do trato urinário. **Pouco frequentes:** Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilação auricular, taquicardia supraventricular e extrasístoles); Irritação da garganta; Broncospasma; Boca seca; Equimose; Retenção urinária; Dor torácica. **Muito raros:** Sinais ou sintomas de efeitos sistémicos de glucocorticóides, por exemplo supressão suprarrenal; Comportamento anormal. **Desconhecido:** Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoar> (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 compartilhado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 1.1 (abril 2022).**

Promovido e comercializado por:

tecmede
TECNIMED - Sociedade Técnico-Medicinal, S.A. - Rua da Tapada Grande, n.º 2 2710-089 ABRUNHEIRA, PORTUGAL
Tel.: +351 210 414 101 | Fax: +351 219 412 157
NIF: 500 826 413
TRIBE231AC/NOV/2022, revoluído anualmente



Titular de AIM e comercialização:

AstraZeneca
AstraZeneca Produtos Farmacêuticos, Lda
R, Humberto Madeira n.º 71 Queluz (Baixo)
2730-097 Barcarena | Contribuinte N.º PT 502 942 240
Capital Social: 1.500.000€ | Mat. Cons. Reg. Com.
Cecilia sob o N.º 509242240
Telefone: +351 214 346 100

ARTIGO ORIGINAL

Efeito a longo prazo da asma no desenvolvimento da obesidade entre os adultos: um estudo de coorte internacional, ECRHS

Subhabrata Moitra,^{1,2,3,4} Anne-Elie Carsin,^{2,3,4} Michael J Abramson,⁵ Simone Accordini,⁶ Andre F S Amaral,⁷ Josep Anto,^{2,3,4} Roberto Bono,⁸ Lidia Casas Ruiz,^{9,10} Isa Cerveri,¹¹ Leda Chatzi,^{12,13,14} Pascal Demoly,^{15,16} Sandra Dorado-Arenas,¹⁷ Bertil Forsberg,¹⁸ Frank Gilliland,¹³ Thorarinn Gislason,^{19,20} Jose A Gullón,²¹ Joachim Heinrich,^{22,23} Mathias Holm,²⁴ Christer Janson,²⁵ Rain Jogi,²⁶ Francisco Gómez Real,^{27,28} Debbie Jarvis,²⁹ Bénédicte Leynaert,^{30,31} Dennis Nowak,²² Nicole Probst-Hensch,^{32,33} José Luis Sánchez-Ramos,³⁴ Chantal Raherison-Semjen,³⁵ Valerie Siroux,³⁶ Stefano Guerra,³⁷ Manolis Kogevinas,^{2,3,4} Judith Garcia-Aymerich^{2,3,4}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2021-217867>).

For numbered affiliations see end of article.

Correspondence to

Dr Subhabrata Moitra, Division of Pulmonary Medicine, Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, AB T6G 2R3, Canada; moitra@ualberta.ca

SM and A-EC contributed equally.

Received 28 June 2021
Accepted 16 March 2022
Published Online First
27 April 2022



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Moitra S, Carsin A-E, Abramson MJ, et al. *Thorax* doi:10.1136/thoraxjnl-2021-217867

RESUMO

Introdução A obesidade é um fator de risco conhecido para a asma. Embora existam indícios de que a asma provoca obesidade nas crianças, a ligação entre a asma e a obesidade não tem sido investigada em adultos.

Métodos Utilizamos os dados do European Community Respiratory Health Survey (ECRHS), um estudo coorte levado a cabo em 11 países europeus e na Austrália em 3 ondas entre 1990 e 2014 em intervalos de cerca de 10 anos. Consideramos dois períodos do estudo: de ECRHS I (t) a ECRHS II (t+1) e de ECRHS II (t) a ECRHS III (t+1). Excluímos os indivíduos obesos (índice de massa corporal ≥ 30 kg/m²) na visita t. O risco relativo (RR) de obesidade em t+1 associado à asma em t foi estimado por uma regressão de Poisson multivariada modificada (lag) com medições repetidas. Além disso, examinamos a associação de atopia e medicação de asma no desenvolvimento da obesidade.

Resultados Incluímos 7576 participantes no período ECRHS I-II [51,5 % mulheres, média de idade (DP) de 34 (7) anos] e 4976 no ECRHS II-III [513 % mulheres, 42 (8) anos]. Nove por cento dos participantes tornaram-se obesos em ECRHS I-II e 15 % em ECRHS II-III. O risco de desenvolver obesidade foi mais elevado entre os asmáticos do que os não asmáticos (RR 1,22, IC 95%, 1,07 a 1,38), e particularmente mais elevado entre os não atópicos do que os atópicos (1,47; 1,17 a 1,86 vs 1,04; 0,86 a 1,27), os que padeciam da doença há mais tempo (1,32; 1,10 a 1,59 há >20 anos vs 1,12; 0,87 a 1,43 há ≤ 20 anos) e os que tomavam corticosteroides orais (1,99; 1,26 a 3,15 vs. 1,15; 1,03 a 1,28). A atividade física não foi um mediador nesta associação.

Conclusão Este é o primeiro estudo que mostra que os adultos asmáticos têm um risco mais elevado de desenvolver obesidade do que os não asmáticos, em especial os não atópicos, que padecem da doença há mais tempo ou que tomam corticosteroides orais.

INTRODUCTION

Several studies demonstrating the coexistence of obesity and asthma across the world suggest the presence of common aetiological factors between these conditions.^{1–5} Asthma and obesity share some common socioeconomic, behavioural and environmental risk factors, all of which could trigger the expression of genes, leading to the development of either of these diseases. Previous studies focused mainly on the mechanisms by which obesity could lead to asthma.

Key messages

What is the key question?

► Although an association between obesity and asthma has been well established, whether asthma can relate to the increased risk of future obesity has only been studied in children.

What is the bottom line?

► Asthmatics, particularly those who were non-atopic, had longer disease duration or were on oral corticosteroids, were at a higher risk of developing obesity later in life. This association was not mediated by physical activity.

Why read on?

► Understanding the crosstalk between asthma and obesity would help set a proper strategy for asthma management, particularly with an emphasis on reducing adverse effects of corticosteroids in asthma treatment.

Several obesity-associated biological phenomena have been proposed, such as by altering the lung compliance (causing airflow limitation), increasing the synthesis of immune-modulators, affecting the sympathetic nervous system or by modulating gene function.^{1,2} The inverse relationship, that is, whether asthma is a risk factor for later obesity had not received much attention until recently.

In a longitudinal cohort study of kindergarten and first-grade children, Chen *et al.* observed that the non-obese children who were diagnosed with asthma during the recruitment phase were at increased risk of developing obesity during the 10 years follow-up.⁶ This was confirmed in a pooled analysis of 18 European cohorts associating physician diagnosed asthma at 3–4 years with incident obesity at 8 years, the risk being higher among children with active asthma symptoms.⁷ Another recent study demonstrated a link between high peak flow variability in childhood and a steeper increase of body mass index (BMI) in adulthood.⁸

Despite studies on children and young adolescents, whether and to what extent asthma increased the risk for subsequent obesity among adults remained unclear. Asthma in adults may be causally and aetiological more complex than childhood asthma (which is predominantly allergic asthma), therefore, the magnitude of the asthma-obesity risk is likely to be different in adults.

In line with the previously reported observations, we hypothesised that asthma could be a risk factor for obesity at a later stage of life. Therefore, we aimed to investigate the occurrence of obesity attributable to asthma in participants of the European Community Respiratory Health Survey (ECRHS) over two period of 10 years.

METHODS

Design and participants

ECRHS is a population-based cohort study initiated in 1990–1994 (ECRHS-I) with over 18 000 participants aged between 20 and 44 years from 30 centres in 14 countries, which had two follow-up rounds at approximately 10-year intervals (ECRHS-II in 1999–2003 and ECRHS-III in 2010–2014). In the recruitment phase, a postal questionnaire was sent containing items about asthma symptoms and exacerbation history in the last 12 months, current medication and allergic conditions such as nasal symptoms and hay fever. From those who responded to the postal questionnaire, participants were either selected from a random sample or a symptomatic sample and were invited for more detailed investigation that included an interviewer-administered questionnaire and lung function testing.^{9–10} The questionnaires and clinical investigations were repeated in the next follow-ups (ECRHS-II and III).

The design and selection of participants of this study are presented in figure 1. We considered two study periods: from ECRHS I (t) to ECRHS II ($t+1$), and from ECRHS II (t) to ECRHS III ($t+1$). At each period we classified the participants as ‘no asthma’ or ‘current asthma’ (see definitions below). To study only incident obesity, we excluded individuals who were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) at visit t . To avoid misclassification in the definition of the ‘current asthma’ and ‘no asthma’ groups, we excluded participants with inactive asthma (ie, self-reported doctor diagnosed asthma, with no respiratory symptoms within the last 12 months). We finally excluded subjects with missing asthma or obesity information at either t or $t+1$, giving a total of 8716 participants from 26 centres of 11 European countries and Australia. Ethical approval of the study was obtained from the ethical review boards or committees of the respective centres. All participants provided signed informed consent. Detailed information about the ethical approval, informed consent and data management were described elsewhere.¹⁰

Definition of asthma-related variables

Asthma-related information was collected at each survey. We defined current asthma as giving a positive answer to the questions ‘Have you ever had asthma?’ and ‘Was this confirmed by a doctor?’, and having reported at least one of the following in the

last 12 months: waking up by an attack of shortness of breath, any asthma attack, or use of asthma medications.^{11–13} Asthma duration at t was derived as the number of years between age at t and reported age at first asthma onset. Atopy was defined as a serum specific IgE antibody concentration of $\geq 0.35 \text{ kU}_A/\text{L}$ to at least one of four common allergens (house dust mite, cat, timothy grass or *Cladosporium herbarum*), as defined previously.¹⁴ We also obtained information on asthma drug treatment from the questions ‘Have you used any pills, capsules, tablets or medicines, other than inhaled medicines, to help your breathing at any time in the last 12 months?’, and defined whether each patient took inhaled (ICS) oral corticosteroids (OCS) or both during the last 12 months. Only at ECRHS II, information was collected on whether OCS were used continuously, for a short-course, or as rescue medication. The modified Medical Research Council (mMRC) Dyspnoea Scale was used to define dyspnoea (considered if they had mMRC grade ≥ 2).¹⁵

Obesity

Height and weight of all participants were measured by physical examination during the clinical visit at each survey. BMI was calculated as weight in kilograms divided by the square of height in metres. Obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$.¹⁶

Other relevant information

At each study wave, we collected data on sociodemographic and other clinical factors using questionnaires. These included sex, age, education (age at which the participants finished their formal education) and smoking status (never, former and current) and intensity (pack-years).

Information about physical activity of the participants was obtained at ECRHS-II and III from a self-completed questionnaire in which they were asked about the weekly frequency and duration of vigorous physical activity.^{17–19} Those who exercised at least two times a week for at least 1 hour were considered physically active.

Statistical analyses

Relative risks (RR) and 95% CIs for the association of current asthma, asthma with atopy, asthma duration, and asthma with medication (ICS, OCS or both), with new obesity onset were estimated using modified Poisson regression for repeated measures with time of follow-up as offset.²⁰ Exposure was the asthma status at the survey time t (lag1) and outcome was obesity at subsequent time $t+1$. Therefore, participants could contribute with one or two observations, that is, from ECRHS-I to ECRHS-II and/or from ECRHS-II to ECRHS-III (figure 1). Multivariate models were fitted after testing the following potential confounders: education, sex, age, smoking status and physical activity (between ECRHS-II and III only). Only those variables associated (ie, $p < 0.05$) both with asthma and obesity were retained. Hence, the final models were adjusted for age, sex and smoking status at time t . Subjects

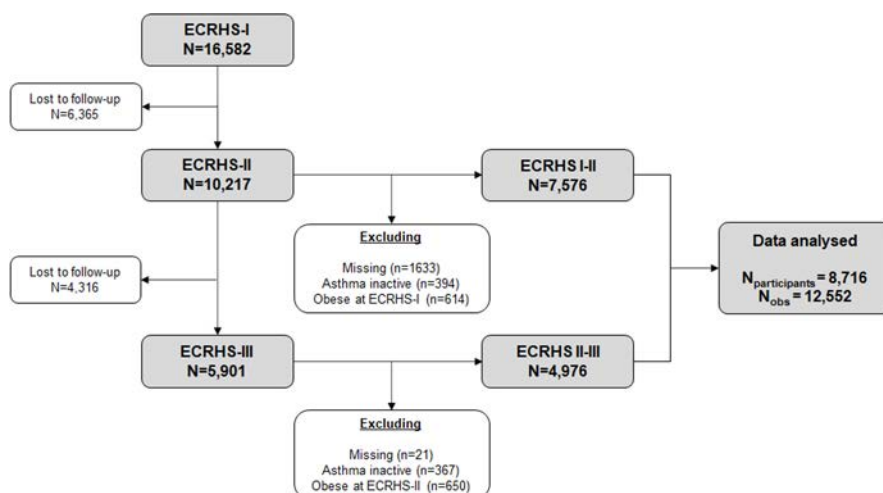


Figure 1 Schematic representation of the study design. ECRHS, European Community Respiratory Health Survey.

Table 1 Demographic profile of the study participants in ECRHS I–II and in ECRHS II–III

	ECRHS I–II n=7576	ECRHS II–III n=4976
Sex (female), n (%)	3905 (51.5)	2555 (51.3)
Age <i>t</i> (years), mean (SD)	34.0 (7.1)	41.5 (7.8)
Age <i>t</i> +1 (years), mean (SD)	42.7 (7.2)	53.9 (7.1)
Education, n (%)		
Low	813 (10.8)	409 (8.5)
Medium	2715 (36.0)	1675 (34.7)
High	4024 (53.3)	2744 (56.8)
Country, n (%)		
Australia	387 (5.1)	212 (4.3)
Belgium	528 (7.0)	287 (5.8)
Estonia	250 (3.3)	132 (2.7)
France	862 (11.4)	737 (14.8)
Germany	534 (7.0)	545 (11.0)
Iceland	434 (5.7)	320 (6.4)
Italy	512 (6.8)	210 (4.2)
Norway	500 (6.6)	298 (6.0)
Spain	1353 (17.9)	806 (16.2)
Sweden	1231 (16.2)	749 (15.1)
Switzerland	483 (6.4)	403 (8.1)
UK	502 (6.6)	277 (5.6)
Smoking status <i>t</i> , n (%)		
Never	3272 (43.3)	2201 (44.4)
Former	2043 (27.0)	1814 (36.6)
Current	2247 (29.7)	939 (19.0)
Current asthma <i>t</i> , n (%)		
No asthma	6859 (90.5)	4495 (90.2)
Current asthma, all	717 (9.5)	490 (9.8)
Current asthma, without atopy	271 (3.6)	190 (3.8)
Current asthma, with atopy	446 (5.9)	300 (6.0)
Current asthma, ≤20 years since onset	406 (5.4)	218 (4.4)
Current asthma, >20 years since onset	308 (4.1)	266 (5.3)
Current asthma, no ICS	494 (6.5)	260 (5.2)
Current asthma, with ICS	223 (2.9)	230 (4.6)
Current asthma, no OCS	664 (8.8)	454 (9.1)
Current asthma, with OCS	53 (0.7)	36 (0.7)
Current asthma, only ICS	183 (2.4)	199 (4.0)
Current asthma, ICS and OCS	40 (0.5)	31 (0.6)
BMI <i>t</i> (kg/m ²), mean (SD)	23.3 (2.8)	24.1 (2.9)
BMI <i>t</i> +1 (kg/m ²), mean (SD)	25.0 (3.6)	26.0 (3.8)
Obesity (yes) <i>t</i> +1, n (%)	655 (8.6)	736 (14.8)
Dyspnoea (yes) <i>t</i> , n (%)	256 (3.4)	182 (3.7)
Physical activity (yes) <i>t</i> +1, n (%)	2627 (37.0)	2029 (41.8)

Current asthma defined as a self-report of a doctor's asthma diagnosis and at least one of the following, within the last 12 months: waking up by an attack of shortness of breath, any asthma attack or use of asthma medications. Individuals with inactive asthma (reporting asthma diagnosis without any current symptoms) were excluded from the study (see the Methods section).

BMI, body mass index; ECRHS, European Community Respiratory Health Survey; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

nested in centre were included as random effects to account for the repeated data design.

Models were presented overall and separately by sex. We performed meta-analysis to determine if there was any heterogeneity between the participating countries and between centres.

Two secondary analyses were performed: (1) to determine if physical activity could be a mediator in the asthma-obesity association, we tested three paths separately: physical activity at ECRHS-II mediating the relationship between asthma at ECRHS-I and obesity at ECRHS-II (path 1), physical activity at ECRHS-II

mediating the relationship between asthma at ECRHS-I and obesity at ECRHS-II (path 2), and physical activity at ECRHS-III mediating the relationship between asthma at ECRHS-II and obesity at ECRHS-III (path 3) and (2) to estimate the impact of smoking cessation on the association between asthma and new obesity onset, we stratified our models by active smokers (at time *t*), smokers who quit during the study (between ECRHS-I and II, and ECRHS-II and III), and never smokers.

Some sensitivity analyses were performed to check the robustness of our results. We repeated our analyses: (1) excluding those who did not take part in all three ECRHS waves; (2) excluding participants who reported avoiding physical activity because of respiratory symptoms; (3) excluding those who reported dyspnoea at time *t*; (4) defining current asthma as the a self-report of doctor's diagnosis and at least one of the following within the last 12 months: waking up by an attack of shortness of breath, any asthma attack, use of asthma medications, wheeze, shortness of breath, waking up with chest tightness or attack of cough and (5) using BMI change between *t* and *t*+1 as the outcome variable in linear mixed regression. All analyses were performed in STATA (V.12.1, StataCorp).

ANALYSIS

Distribution of the participants included in this analysis is presented in table 1. We studied 7576 participants in the period ECRHS I–II (51.5% female, mean (SD) age of 34 (7) years at ECRHS I) and 4976 participants in the period ECRHS II–III (51.3% female, 42 (8) years at ECRHS II). Current smokers decreased during follow-up (30% in ECRHS I–II vs 19% in ECRHS II–III). The relative number of participants with current asthma remained the same across the study waves. Overall, 9% of participants became obese from ECRHS-I to ECRHS-II and this proportion rose to 15% from ECRHS II to ECRHS-III. We observed that 37% of the study population was physically active at ECRHS-II which increased slightly to 42% at ECRHS-III.

The association between asthma and obesity is presented in online supplemental table E1 and figure 2. Compared with 8.4% and 14.6% of non-asthmatics who developed obesity at ECRHS-II and ECRHS-III, respectively, 10.7% and 16.9% asthmatics developed obesity at ECRHS-II and III. The absolute risk difference in asthmatics vs no asthmatics was 2.3% (95% CI 0.8% to 3.9%) and the RR was 1.21 (95% CI 1.07 to 1.37). After adjusting for potential confounders (age, sex and smoking status at time *t*), the association between asthma and the development of obesity remained significant (1.22; 95% CI 1.07 to 1.38). The association was stronger among asthmatics without atopy (1.47; 95% CI 1.17 to 1.86), asthmatics with longer disease duration (1.32; 95% CI 1.10 to 1.59), asthmatics who used OCS (1.99; 95% CI 1.26 to 3.15) and those who used both OCS and ICS (2.07; 95% CI 1.19 to 3.59).

We conducted post hoc analyses to understand better the association between OCS intake and incident obesity. The comparison between patients on continuous, short course or use as rescue medication of OCS suggested a higher risk of obesity among those using continuously, but very small sample size precluded any kind of statistical testing (online supplemental table E2).

The association of asthma and obesity was similar in males (1.27; 95% CI 1.06 to 1.51) and females (1.20; 95% CI 1.01 to 1.42, online supplemental table E3). The association of asthma with new-onset obesity was homogeneous across the participating countries (figure 3) and centres (online supplemental figure E1). The overall estimates from the meta-analyses were similar to that reported in the main analysis and there was no statistical evidence of heterogeneity ($I^2=0$, *p* values for heterogeneity were 0.70 and 0.96 for country and centre, respectively).

No evidence of physical activity as a mediator in the asthma-obesity association was observed (online supplemental table E4). When stratified by smoking status, the risk of becoming obese in asthmatics was higher among current smokers (1.46, 95% CI 1.12 to 1.90) and among never smokers (1.27, 95% CI 1.08 to 1.49), while no association between asthma and obesity was observed among those who stopped smoking (0.95; 95% CI 0.65 to 1.37)

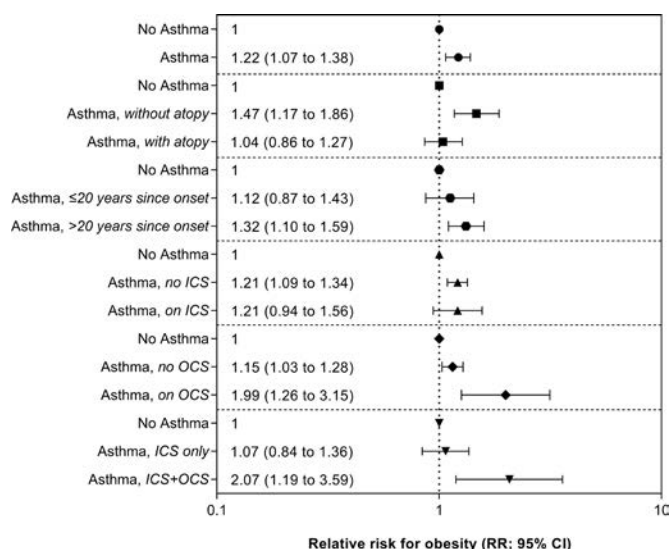


Figure 2 Association between asthma, asthma with atopy, asthma duration and asthma with medication at t and incident obesity at $t+1$. Data presented as relative risk (RR) and 95% CI. RR was calculated from modified poisson regression with robust SEs and subjects nested in centre as random effects. All models (for all participants) were adjusted for age, sex and smoking status at time t . See full figures in online supplemental table E1. ICS, inhaled corticosteroids; OCS, oral corticosteroids.

(online supplemental table E5). In the sensitivity analyses, the estimates were comparable to the main analyses (online supplemental tables E6–E10).

DISCUSSION

In this prospective cohort study, we found that individuals with active asthma were at higher risk of developing obesity compared with individuals without asthma, that this association was higher among non-atopic asthmatics, those with long disease duration or those using OCS, and that the association was not mediated by physical activity levels.

Our observation of accelerated weight gain among asthmatics is supported by a previous prospective study that demonstrated asthma to be associated with increased weight gain at a later stage in women,²¹ although unlike our results, they did not find any such association in men. Two recent longitudinal studies in children, one of them including more than 21 000 children from 16 European cohorts, showed that childhood asthma was a risk factor for obesity at a later age.^{6,7} Another recent report also demonstrated that children with high peak flow variability were on a steeper increase of BMI up to young adult life that was not associated with asthma.⁸ This evidence suggests that asthma and obesity share several common physiological pathways and a bidirectional association between asthma and obesity is plausible.

It has been debated whether there is any association between atopy and increased body weight.²² While several reports support this association,^{23–24} other studies have shown that the risk of being overweight is higher among the non-atopic than those with marked allergic sensitisation.^{25,26} Our observation of a greater risk of obesity among non-atopic asthmatics indicates that allergic sensitisation is unlikely to explain the association between asthma and obesity.

We observed that the risk of developing obesity was more pronounced among asthmatics who were on OCS than those who were not, in agreement with previous reports, in adults and children with asthma, relating the intake of OCS with abnormal weight gain.^{27–30} Unfortunately, we could not test the role of corticosteroids dose or duration due to small sample size of OCS users. The effects of long-term use of OCS on weight gain are well established in asthma and general population,^{27,31} and supported by several mechanisms, including but not limited to increased lipid uptake from the gut and storing in the peripheral tissues,³⁰ or

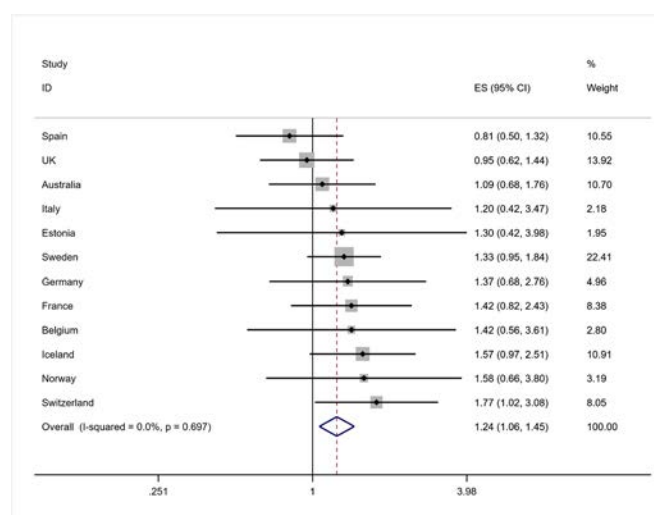


Figure 3 Meta-analysis results of the association between asthma at t and obesity at $t+1$ by country.

increased insulin resistance.³² However, we also found an increased and statistically significant risk of obesity among asthmatics who reported not having taken OCS. One could argue that, if asthma really causes weight gain, this effect would be higher among those with severe asthma, so the higher risk observed among OCS users is actually the result of confounding by indication and not a result of the treatment itself.³³ This is supported by our findings of higher obesity risk among asthmatics of longer disease duration.

A potential explanation for asthma causing weight gain is through the reduction of physical activity levels. Patients with chronic respiratory diseases tend to be less physically active due to recurrent episodes of breathlessness or persistent wheezing.³⁴ However, our analyses do not support this hypothesis, as physical activity was not mediating the asthma–obesity association and this association remained after excluding those participants who did not perform physical activity due to breathlessness, in line with the previously mentioned study among asthmatic children who developed obesity on follow-up independent of physical activity.⁶

Another potential explanation would be the role of smoking. Smoking cessation has been observed to augment weight gain at least in the short term.^{35,36} However, we found no association between asthma and incident obesity among participants who had quit smoking. On the contrary, we observed greater RRs among current smokers and non-smokers. Smoking has been observed to reduce the efficacy of steroid treatment in asthma,^{37–39} so it could be argued that asthmatics who smoke are at a higher risk of the effects of asthma (such as obesity) because of worse disease control. All these suggest that there may be mechanisms other than OCS use, reducing physical activity and smoking cessation, linking asthma to obesity, but these are yet unknown.

Our study outcomes are of significant clinical importance. First, our observation of higher obesity risk in asthmatics who took OCS, advocates the minimal and precise use of OCS in asthma.⁴⁰ Although current recommendations of OCS for asthma management, several reports also indicate that oral steroids are still prescribed indiscriminately in asthma, sometimes, even without diagnosing the severity of the disease properly.^{41–43} This could result in an increasing burden of adverse health effects in asthma, obesity being one of the major consequences. Second, the observation of a greater risk of obesity among non-atopic asthmatics directs our attention towards adult-onset asthma and supports increasing attention to the reduction of adult risk factors, such as occupational exposures that account for up to 25% of adult-onset asthma.⁴⁴ Third, we also observed a higher risk of obesity among asthmatics who were smokers. Although smoking cessation programmes have now become a part of the clinical management of respiratory and cardiovascular diseases, evidence shows that not all patients benefit from them, particularly in primary care.^{45,46} Advice on smoking cessation along with its plausible consequences

(such as temporary weight gain) should also be discussed with the patients. Finally, although we did not find any evidence of physical activity mediating the asthma-obesity interaction, it must be noted that lifestyle factors also significantly influence weight gain. Thus, advice on healthy diet, proper physical activity and lifestyle modification should be warranted as part of asthma management.

The strengths of our study included its longitudinal design, allowing the exclusion of obese subjects at baseline, with a large cohort that was followed over a long period of time. Furthermore, we performed several sensitivity analyses to test the robustness of our results against assumptions about asthma or obesity misclassification, residual confounding or model misspecification. Lastly, the results were homogeneous across the participating countries which indicate that study findings can be extrapolated to other populations.

A limitation in this study is the potential bias in defining asthma and obesity status, given the lack of information on when events happened during the 10 years follow-up period. However, our results were robust to several sensitivity analyses. Although we were able to consider plausible known confounders, the effect of other lifestyle factors (such as diet, only available in a subsample of ECRHS at one single time point), psychosocial attributes, or genetic predisposition could not be analysed. Finally, we were limited to explore in detail the role of OCS on obesity risk because of the lack of detailed information on dosage, duration or their use for other diseases than asthma.

CONCLUSION

In summary, we demonstrated that participants with asthma were at a higher risk of developing obesity later in life and the risk was more pronounced among those asthmatics who were non-atopic, those with asthma of longer duration and those on OCS. These results support earlier results in children and warrant further clinico-epidemiological and experimental research, in order to determine the mechanisms through which asthma could trigger obesity risk among adults.

Author affiliations

¹Division of Pulmonary Medicine, Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada

²Non-Communicable Diseases and Environment Programme, ISGlobal, Barcelona, Spain

³Universitat Pompeu Fabra (UPF), Barcelona, Spain

⁴CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

⁵School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

⁶Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy

⁷National Heart and Lung Institute, Imperial College London, London, UK

⁸Department of Public Health and Pediatrics, University of Turin, Torino, Italy

⁹Epidemiology and Social Medicine, University of Antwerp, Antwerpen, Belgium

¹⁰Centre for Environment and Health, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

¹¹Unit of Respiratory Diseases, IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

¹²Department of Social Medicine, University of Crete, Rethimno, Greece

¹³Department of Preventive Medicine, USC Keck School of Medicine, Los Angeles, California, USA

¹⁴Department of Genetics & Cell Biology, Maastricht University, Maastricht, The Netherlands

¹⁵Department of Pulmonology, Division of Allergy, University Hospital of Montpellier, Montpellier, France

¹⁶Inserm, Sorbonne Université, Equipe, EPAR - IPLESP, Paris, France

¹⁷Osakidetza Basque Health Service, Department of Respiratory Medicine, Galdakao University Hospital, Galdakao, Spain

¹⁸Section of Sustainable Health, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

¹⁹Department of Sleep, Landspítali - The National University Hospital of Iceland, Reykjavik, Iceland

²⁰Faculty of Medicine, University of Iceland, Reykjavik, Iceland

²¹Department of Pneumology, University Hospital San Agustín, Avilés, Spain

²²Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Ludwig Maximilians University Munich, University Hospital Munich, Munich, Germany

²³Institut of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Oberschleissheim, Germany

²⁴Department of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

²⁵Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

²⁶Lung Clinic, Tartu University Hospital, Tartu, Estonia

²⁷Department of Gynaecology and Obstetrics, Haukeland University Hospital, Bergen, Norway

²⁸Department of Clinical Science, University of Bergen, Bergen, Norway

²⁹MRC Centre for Environment and Health, Imperial College London, London, UK

³⁰Inserm - U1168, VIMA (Aging and Chronic Diseases: Epidemiological and Public Health Approaches), INSERM, Villejuif, France

³¹UMR-S 1168, Université de Versailles Saint-Quentin-en-Yvelines - UVSQ, Saint-Quentin-en-Yvelines, France

³²Department Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland

³³Department of Clinical Research, University of Basel, Basel, Switzerland

³⁴Department of Nursing, University of Huelva, Huelva, Spain

³⁵INSERM U1219, Institute of Public Health and Epidemiology, CHU de Bordeaux, Bordeaux, France

³⁶Team of Environmental Epidemiology, Inserm U1209, Univ Grenoble Alpes, La Tronche, France

³⁷Arizona Respiratory Center, University of Arizona Medical Center - University Campus, Tucson, Arizona, USA

³⁸Twitter Subhadrata Moitra @Subha_Moitra

Collaborators ECRHS I Co-ordinating Centre (London): P Burney, S Chinn, C Luczynska, D Jarvis, E Lai. Project Management Group: P Burney (Project leader-UK), S Chinn (UK), C Luczynska (UK), D Jarvis (UK), P Vermeiret (Antwerp), H Kesteloot (Leuven), J Bousquet (Montpellier), D Nowak (Hamburg), J Pridhardt (Dublin), R de Marco (Verona), B Rijcken (Groningen), JM Antó (Barcelona), J Alves (Oporto), G Boman (Uppsala), N Nielsen (Copenhagen), P Paoletti (Pisa). ECRHS II Steering Committee: U Ackermann-Lieblich (University of Basel, Switzerland); N. Kuenzi

(University of Basel, and University of Southern California, Los Angeles, USA); J.M. Antó and J. Sunyer (Institut Municipal d' Investigació Mèdica (IMIM-IMAS), Universitat Pompeu Fabra (UPF), Spain); P. Burney (project leader), S Chinn, D. Jarvis, J. Knox and C. Luczynska (King's College London, UK); J. Cerveri (University of Pavia, Italy); R. de Marco (University of Verona, Italy); T. Gislason (Iceland University Hospital, Iceland); J. Heinrich and M. Wjst (GSF-Institute of Epidemiology, Germany); C. Janson (Uppsala University, Sweden); B. Leynaert and F. Neukirch (Institut National de la Santé et de la Recherche Médicale (INSERM), France); J. Schouten (University of Groningen, The Netherlands); C. Svane (University of Bergen, Norway); P. Vermeiret (University of Antwerp, Belgium). Principal Investigators and senior scientific teams: Australia: (M. Abramson, E.H. Walters, J. Raven); Belgium: South Antwerp and Antwerp City (P. Vermeire, J. Weyler, M. van Sprundel, V. Nelen); Estonia: Tartu (R. Jögi, A. Soon); France: Paris (F. Neukirch, B. Leynaert, R. Liard, M. Zureik), Grenoble (I. Pin, J. Ferran-Quentin), Bordeaux (A. Teyssie, C. Raherison), Montpellier (J. Bousquet, P. Bousquet); Germany: Erfurt (J. Heinrich, M. Wjst, C. Frye, I. Meyer); Iceland: Reykjavik (T. Gislason, E. Björnsson, D. Gislason, K.B. Jörundsdóttir); Italy: Turin (R. Bono, M. Bugiani, P. Piccioni, E. Caria, A. Carosso, E. Migliore, G. Castiglioni), Verona (R. de Marco, G. Verlate, E. Zanolin, S. Accordini, A. Poli, V. Lo Cascio, M. Ferrari, I. Cazzolletti), Pavia (A. Marinoni, S. Villani, M. Ponzio, F. Frigerio, M. Comelli, M. Grassi, I. Cerveri, A. Corsico); Norway: Bergen (A. Gulsvik, E. Omenaas, C. Svane, B. Laerum); Spain: Albacete (J. Martínez-Moratalla Rovira, E. Almar, M. Arévalo, C. Boix, G. González, J.M. Ignacio García, J. Solera, J. Damián), Galdakao (N. Muñozguren, J. Ramos, I. Urrutia, U. Aguirre), Barcelona (J. M. Antó, J. Sunyer, M. Kogevinas, J. P. Zock, X. Basagaña, A. Jaen, F. Burgos, C. Acosta), Huelva (I. Maldonado, A. Pereira, J.L. Sánchez), Oviedo (F. Payo, I. Huerta, A. de la Vega, I. Palenciano, J. Azofra, A. Cañada); Sweden: Göteborg (K. Torén, L. Lilienberg, A. C. Olin, B. Balder, A. Pfeifer-Nilsson, R. Sundberg), Umeå (E. Norrman, M. Soderberg, K.A. Franklin, B. Lundback, B. Forsberg, L. Nystrom), Uppsala (C. Janson, G. Boman, D. Norback, G. Wieslander, M. Gunnbjörnsdóttir); Switzerland: Basel (N. Kuenzi, B. Dibbert, M. Hazenkamp, M. Brutsche, U. Ackermann-Lieblich); United Kingdom: Ipswich (D. Jarvis, R. Hall, D. Seaton), Norwich (D. Jarvis, B. Harrison). ECRHS II Principal Investigators and senior scientific teams: Australia: Melbourne (M. Abramson, G. Benke, S. Dharmage, B. Thompson, S. Kaushik, M. Matheson), Belgium: South Antwerp & Antwerp City (J. Weyler, H. Bentouhami, V. Nelen), Estonia: Tartu (R. Jögi, H. Oros), France: Bordeaux (C. Raherison, P.O. Girodet), Grenoble (I. Pin, V. Siroux, J. Ferran, J.L. Cracowski), Montpellier (P. Demoly, A. Bourdin, I. Vachier), Paris (B. Leynaert, D. Soussan, D. Courbon, C. Neukirch, L. Alavoine, X. Duval, I. Poirier), Germany: Erfurt (J. Heinrich, E. Becker, G. Woelke, O. Manuwalid), Hamburg (H. Magnussen, D. Nowak, A.-M. Kirsten), Iceland: Reykjavik (T. Gislason, B. Benediktsson, D. Gislason, E.S. Arnardottir, M. Clausen, G. Gudmundsson, L. Gudmundsdóttir, H. Palsdottir, K. Olafsdottir, S. Sigurdsson, K. Bara-Jörundsdóttir), Italy: Pavia (I. Cerveri, A. Corsico, A. Grossi, F. Albinici, E. Gini, E.M. Di Vincenzo, V. Ronzoni, S. Villani, F. Campanella, M. Gnesi, F. Manzoni, L. Rossi, O. Ferraro), Turin (M. Bugiani, R. Bono, P. Piccioni, R. Tassinari, V. Bellisario, G. Trucco), Verona (R. de Marco, S. Accordini, L. Calciano, L. Cazzolletti, M. Ferrari, A.M. Fratta Pasini, F. Locatelli, P. Marchetti, A. Marcon, E. Montoli, G. Nguyen, M. Olivieri, C. Papadopoulou, C. Posenato, G. Pesce, P. Vallerio, G. Verlate, E. Zanolin), Norway: (C. Svane, E. Omenaas, A. Johannessen, T. Skorge, F. Gomez Real), Spain: Albacete (J. Martínez-Moratalla Rovira, E. Almar, A. Mateos, S. García, A. Núñez, P. López, R. Sánchez, E. Mancebo), Barcelona (J.-M. Antó, J.P. Zock, J. García-Aymerich, M. Kogevinas, X. Basagaña, A.E. Carsin, F. Burgos, C. Sanjuas, S. Guerra, B. Jacquemin, P. David), Galdakao (N. Muñozguren, I. Urrutia, U. Aguirre, S. Pascual), Huelva (J. Antonio Maldonado, A. Pereira, J. Luis Sánchez, L. Palacios, Oviedo: (F. Payo, I. Huerta, N. Sánchez, M. Fernández, B. Robles), Sweden: Göteborg (K. Torén, M. Holm, J.-L. Kim, A.-C. Olin, A. Dahlman-Högstrand), Umeå (B. Forsberg, L. Braback, L. Modig, B. Järholm, H. Bertilsson, K.A. Franklin, C. Wahlgreen), Uppsala: (B. Andersson, D. Norback, U. Spetz Nystrom, G. Wieslander, G.M. Bodina Lund, K. Nisser); Switzerland: Basel (N.M. Probst-Hensch, N. Künzli, D. Stolz, C. Schindler, T. Rochat, J.M. Gaspoz, E. Zemp Stutz, M. Adam, C. Autenrieth, I. Curjuric, J. Dratva, A. Di Pasquale, R. Ducret-Stich, E. Fischer, L. Grize, A. Hensel, D. Keidel, A. Kumar, M. Imboden, N. Maire, A. Mehta, H. Phuleria, M. Ragetti, M. Ritter, E. Schaffner, G.A. Thun, A. Ineichen, T. Schikowski, M. Tarantino, M. Tsai, UK: London (P. Burney, D. Jarvis, S. Kapur, R. Newton, J. Potts), Ipswich: (N. Innes), Norwich: (A. Wilson).

Contributors SM, A-EC, MK and JG-A conceived the study design, analysed the results, interpreted the data, and drafted the manuscript. SG interpreted the data; drafted the article or revised it; provided intellectual content of critical importance to the work described. All other authors revised the manuscript and provided critical comments. SM, A-EC, and JG-A are the guarantors and accept full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The following grants helped to fund the local studies: Australia: Asthma Foundation of Victoria, Allen and Hanbury's, Belgium: Belgian Science Policy Office, National Fund for Scientific Research, Estonia: Estonian Science Foundation, grant no 1088, France: Ministère de la Santé, Glaxo France, Institut Pneumologique d'Aquitaine, Contrat de Plan Etat-Région Languedoc-Roussillon, CNMATS, CNMRT (90MR/10, 91AF/6), Ministère délégué de la santé, RNSP, France; GSF, Germany: Bundesministerium für Forschung und Technologie, Italy: Ministero dell'Università e della Ricerca Scientifica e Tecnologica, CNR, Regione Veneto grant RSF n. 381/05.93, Norway: Norwegian Research Council project no. 101422/310, Spain: Fondo de Investigación Sanitaria #91/0016-060-05/E, 92/0319 and #93/0393, the Spanish General de Albacete, Hospital General Juan Ramón Jiménez, Dirección Regional de Salud Pública (Consejería de Sanidad del Principado de Asturias), CIRIT (1997 SGR 00079) and Servicio Andaluz de Salud, Sweden: The Swedish Medical Research Council, the Swedish Heart Lung Foundation, the Swedish Association against Asthma and Allergy, Switzerland: Swiss national Science Foundation grant 4026-28099, UK: National Asthma Campaign, British Lung Foundation, Department of Health, South Thames Regional Health Authority. Coordination: The co-ordination of this work was supported by the European Commission and the authors and participants are grateful to the late C. Baya and M. Hallen for their help during the study and K. Vuytsteek and the members of the COMAC for their support. Financial Support: Australia: National Health and Medical Research Council; Belgium: Antwerp: Fund for Scientific Research (grant code, G.0402.00), University of Antwerp, Flemish Health Ministry; Estonia: Tartu Estonian Science Foundation grant no 4350; France: (All) Programme Hospitalier de Recherche Clinique—Direction de la Recherche Clinique (DRC) de Grenoble 2000 number 2610, Ministry of Health, Ministère de l'Emploi et de la Solidarité, Direction Générale de la Santé, Centre Hospitalier Universitaire (CHU) de Grenoble, Bordeaux: Institut Pneumologique d'Aquitaine, Grenoble: Comité des Maladies Respiratoires de l'Isère, Montpellier: Aveniris (France), Direction Régionale des Affaires Sanitaires et Sociales Languedoc-Roussillon, Paris: Union Chimique Belge- Pharma (France), Aveniris (France), Glaxo France; Germany: Erfurt GSF—National Research Centre for Environment and Health, Deutsche Forschungsgemeinschaft (grant code, FR1526/1-1), Hamburg: GSF—National Research Centre for Environment and Health, Deutsche Forschungsgemeinschaft (grant code, MA 711/4-1); Iceland: Reykjavik, Icelandic Research Council, Icelandic University Hospital Fund; Italy: Pavia GlaxoSmithKline Italy, Italian Ministry of University and Scientific and Technological Research (MURST), Local University Funding for Research 1998 and 1999, Turin: Azienda Sanitaria Locale 4 Regione Piemonte (Italy), Azienda Ospedaliera Centro Traumatologico Ospedaliero Centro Traumatologico Ortopedico—Istituto Clinico Ortopedico Regina Maria Adelaide Regione Piemonte, Verona: Ministero dell'Università e della Ricerca Scientifica (MURST), Glaxo Wellcome spa; Norway: Bergen: Norwegian Research Council, Norwegian Asthma and Allergy Association, Glaxo Wellcome AS, Norway Research Fund; Spain: Fondo de Investigación Sanitaria (grant codes, 97/0035-01, 99/0034-01 and 99/0034-02), Hospital Universitario de Albacete, Consejería de Sanidad, Barcelona: Sociedad Española de Neumología y Cirugía Torácica, Public Health Service (grant code, R01 HL62633-01), Fondo de Investigaciones Sanitarias (grant codes, 97/0035-01, 99/0034-01, and 99/0034-02), Consell Interdepartamental de Recerca i Innovació Tecnològica (grant code, 1999SGR 00241) Instituto de Salud Carlos III; Red de Centros de Epidemiología y a Salud Pública, C03/09, Red de Bases moleculares y fisiológicas de las Enfermedades Respiratorias, C03/01 and Red de Grupos Infancia y Medio Ambiente G03/176, Huelva: Fondo de Investigaciones Sanitarias (grant codes, 97/0035-01, 99/0034-01, and 99/0034-02), Galdakao: Basque Health Department, Oviedo: Fondo de Investigaciones Sanitarias (97/0035-02, 97/0035, 99/0034-01, 99/0034-02, 99/0034-04, 99/0034-06, 99/350, 99/0034-07), European Commission (EU-PEAL P101237), Generalitat de Catalunya (CIRIT 1999 SGR 00214), Hospital Universitario de Albacete, Sociedad Española de Neumología y Cirugía Torácica (SEPAR R01 HL62633-01) Red de Centros de Epidemiología y Salud Pública (C03/09), Red de Bases moleculares y fisiológicas de las Enfermedades Respiratorias (C03/01) and Red de Grupos Infancia y Medio Ambiente (G03/176); 97/0035-01, 99/0034-01, and 99/0034-02); Sweden: Göteborg, Umeå, Uppsala: Swedish Heart Lung Foundation, Swedish Foundation for Health Care Sciences and Allergy Research, Swedish Asthma and Allergy Foundation, Swedish Cancer and Allergy Foundation, Swedish Council for Working Life and Social Research (FAS); Switzerland: Basel Swiss National Science Foundation, Swiss Federal Office for Education and Science, Swiss National Accident Insurance Fund; UK: Ipswich and Norwich: Asthma UK (formerly known as National Asthma Campaign). Coordination: The coordination of this work was supported by the European Commission, as part of their Quality of Life programme, (Grant code: QL4A-CT-1999-01237). Financial Support: Australia: National Health & Medical Research Council, Belgium: Antwerp South, Antwerp City: Research Foundation Flanders (FWO), grant code G.0.410.08.N.10 (both sites). Estonia: Tartu: SF0180060509 from the Estonian Ministry of Education. France: (All) Ministère de la Santé, Programme Hospitalier de Recherche Clinique (PHRC) national 2010, Bordeaux: INSERM U897 Université Bordeaux segalen, Grenoble: Comité Scientifique AGIRadom 2011, Paris: Agence Nationale de la Santé, Région Ile de France, domaine d'intérêt majeur (DIM). Germany: Erfurt: German Research Foundation HE 3294/10-1 Hamburg: German Research Foundation MA 711/6-

1, NO 262/7-1. Iceland: Reykjavik, The Landspítali University Hospital Research Fund, University of Iceland Research Fund, ResMed Foundation, California, USA, Orkuveita Reykjavíkur (Geothermal plant), Vegagerðin (The Icelandic Road Administration (ICERA). Italy: All Italian centres were funded by the Italian Ministry of Health, Chiesi Farmaceutici SpA, in addition Verona was funded by Cariverona foundation, Education Ministry (MIUR). Norway: Norwegian Research council grant no 214123, Western Norway Regional Health Authorities grant no 911631, Bergen Medical Research Foundation. Spain: Fondo de Investigación Sanitaria (PS09/02457, PS09/00716, PS09/01511, PS09/02185, PS09/03190), Servicio Andaluz de Salud, Sociedad Española de Neumología y Cirugía Torácica (SEPAR 1001/2010). Fondo de Investigación Sanitaria (PS09/02457), Barcelona: Fondo de Investigación Sanitaria (FIS PS09/00716), Galdakao: Fondo de Investigación Sanitaria (FIS 09/01511) Huelva: Fondo de Investigación Sanitaria (FIS PS09/02185) and Servicio Andaluz de Salud Oviedo: Fondo de Investigación Sanitaria (FIS PS09/03190). Sweden: All centres were funded by The Swedish Heart and Lung Foundation, The Swedish Asthma and Allergy Association, The Swedish Association against Lung and Heart Disease, Swedish Research Council for health, working life and welfare (FORTE) Göteborg: Also received further funding from the Swedish Council for Working life and Social Research. Umea also received funding from Vasterbotten Country Council ALF grant. Switzerland: The Swiss National Science Foundation (grants no 33CSO-134276/1, 33CSO-108796, 3247BO-104283, 3247BO-104288, 3247BO-104284, 3247-065896, 3100-059302, 3200-052720, 3200-042532, 4026-028099) The Federal office for forest, environment and landscape, The Federal Office of Public Health, The Federal Office of Roads and Transport, the canton's government of Aargau, Basel-Stadt, Basel-Land, Geneva, Luzern, Ticino, Valais and Zürich, the Swiss Lung League, the canton's Lung League of Basel Stadt/ Basel, Landschaft, Geneva, Ticino, Valais and Zürich, SUVA, Freiwillige Akademische Gesellschaft, UBS Wealth Foundation, Talecris Biotherapeutics GmbH, Abbott Diagnostics, European Commission 018996 (GABRIEL), Wellcome Trust WT 084703MA. UK: Medical Research Council (Grant Number 92091). Support also provided by the National Institute for Health Research through the Primary Care Research Network. Coordination: The coordination was funded through the Medical Research Council (Grant Number 92091).

Competing interests SM reports Long-Term Research fellowship and Young Scientist Sponsorship from the European Respiratory Society, outside the submitted work. MJA holds investigator-initiated grants for unrelated research from Pfizer and Boehringer-Ingelheim. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi and has also received a speaker's fee from GSK, outside the submitted work. PD reports personal fees from ALK, Stallergenes Greer, IQVIA, Chiesi, AstraZeneca, Thermo Fisher Scientific, Ménarini, Bausch & Lomb, Mylan, ASIT Biotech, Novartis, Sanofi, Regeneron, outside the submitted work. RJ reports grants from Estonian Research Council Personal Research Grant no 562, during the conduct of the study; personal fees from Consultancy, grants from Grants/grants pending, personal fees from Payment for lectures, personal fees from Travel/accommodations/meeting expenses, outside the submitted work. CR-S reports personal fees from ALK, Astra Zeneca, GSK, Novartis, outside the submitted work.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Regional Ethical Review Board in Uppsala-Sweden (multicentre: Uppsala, Umeå and Göteborg) clinical (Dnr 2016/ 023). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs

Subhabrata Moitra <http://orcid.org/0000-0002-9388-425X>
Michael J Abramson <http://orcid.org/0000-0002-9954-0538>
Simone Accordini <http://orcid.org/0000-0003-1510-6193>
Andre F S Amaral <http://orcid.org/0000-0002-0369-9449>
Sandra Dorado-Arenas <http://orcid.org/0000-0002-0798-2153>
Jose A Gullón <http://orcid.org/0000-0002-3007-0873>
Joachim Heinrich <http://orcid.org/0000-0002-9620-1629>
Christer Janson <http://orcid.org/0000-0001-5093-6980>
Debbie Jarvis <http://orcid.org/0000-0002-1753-3896>
Stefano Guerra <http://orcid.org/0000-0001-7218-3246>
Judith Garcia-Aymerich <http://orcid.org/0000-0002-7097-4586>

REFERENCES

- Ford ES, Mannino DM, Redd SC, et al. Body mass index and asthma incidence among USA adults. *Eur Respir J* 2004;24:740–4.
- Ali Z, Ulrik CS. Obesity and asthma: a coincidence or a causal relationship? A systematic review. *Respir Med* 2013;107:1287–300.
- Schatz M, Zeiger RS, Zhang F, et al. Overweight/obesity and risk of seasonal asthma exacerbations. *J Allergy Clin Immunol Pract* 2013;1:618–22.
- Newson RB, Jones M, Forsberg B, et al. The association of asthma, nasal allergies, and positive skin prick tests with obesity, leptin, and adiponectin. *Clin Exp Allergy* 2014;44:250–60.
- Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;141:1169–79.
- Chen Z, Salam MT, Alderete TL, et al. Effects of childhood asthma on the development of obesity among school-aged children. *Am J Respir Crit Care Med* 2017;195:1181–8.
- Contreras ZA, Chen Z, Roumeliotaki T, et al. Does early onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts. *Eur Respir J* 2018;52 pii: 1800504:1800504.
- Lombardi E, Stern DA, Sherrill D, et al. Peak flow variability in childhood and body mass index in adult life. *J Allergy Clin Immunol* 2019;143:1224–6.
- Burney PG, Luczynska C, Chinn S, et al. The European community respiratory health survey. *Eur Respir J* 1994;7:954–60.

- Jarvis D, Newson R, Janson C, et al. Prevalence of asthma-like symptoms with ageing. *Thorax* 2018;73:37–48.
- de Marco R, Marcon A, Jarvis D, et al. Prognostic factors of asthma severity: a 9-year International prospective cohort study. *J Allergy Clin Immunol* 2006;117:1249–56.
- Cazzoletti L, Marcon A, Corsico A, et al. Asthma severity according to global initiative for asthma and its determinants: an international study. *Int Arch Allergy Immunol* 2010;151:70–9.
- Janson C, Accordini S, Cazzoletti L, et al. Pharmacological treatment of asthma in a cohort of adults during a 20-year period: results from the European community respiratory health survey I, II and III. *ERJ Open Res* 2019;5:00073–2018.
- Le Moual N, Carsin A-E, Siroux V, et al. Occupational exposures and uncontrolled adult-onset asthma in the European community respiratory health survey II. *Eur Respir J* 2014;43:374–86.
- Bestall JC, Paul EA, Garrod R, et al. Usefulness of the medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–6.
- Chinn S, Jarvis D, Melotti R, et al. Smoking cessation, lung function, and weight gain: a follow-up study. *Lancet* 2005;365:1629–35.
- Washburn RA, Goldfield SR, Smith KW, et al. The validity of self-reported exercise-induced sweating as a measure of physical activity. *Am J Epidemiol* 1990;132:107–13.
- Rovio S, Käreholt I, Helkala E-L, et al. Leisure-Time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol* 2005;4:705–11.
- Fuertes E, Markevych I, Jarvis D, et al. Residential air pollution does not modify the positive association between physical activity and lung function in current smokers in the ECRHS study. *Environ Int* 2018;120:364–72.
- Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702–6.
- Hasler G, Gergen PJ, Ajdacic V, et al. Asthma and body weight change: a 20-year prospective community study of young adults. *Int J Obes* 2006;30:1111–8.
- Boulet L-P. Obesity and atopy. *Clin Exp Allergy* 2015;45:75–86.
- Chen Y, Rennie D, Cormier Y, et al. Association between obesity and atopy in adults. *Int Arch Allergy Immunol* 2010;153:372–7.
- Luo X, Xiang J, Dong X, et al. Association between obesity and atopic disorders in Chinese adults: an individually matched case-control study. *BMC Public Health* 2013;13:12.
- von Mutius E, Schwartz J, Neas LM, et al. Relation of body mass index to asthma and atopy in children: the National health and nutrition examination study III. *Thorax* 2001;56:835–8.
- Visness CM, London SJ, Daniels JL, et al. Association of childhood obesity with atopic and nonatopic asthma: results from the National health and nutrition examination survey 1999–2006. *J Asthma* 2010;47:822–9.
- Sullivan PW, Ghushchyan VH, Globe G, et al. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol* 2018;141:110–6.
- Cooper V, Metcalf L, Versnel J, et al. Patient-Reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med* 2015;25:15026.
- Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the optimum patient care research database and the British thoracic difficult asthma registry. *Thorax* 2016;71:339–46.
- Umlawska W. Adipose tissue content and distribution in children and adolescents with bronchial asthma. *Respir Med* 2015;109:200–7.
- Berthon BS, MacDonald-Wicks LK, Wood LG. A systematic review of the effect of oral glucocorticoids on energy intake, appetite, and body weight in humans. *Nutr Res* 2014;34:179–90.
- Carpaiaj OA, van den Berge M. The asthma-obesity relationship: underlying mechanisms and treatment implications. *Curr Opin Pulm Med* 2018;24:42–9.
- Garcia-Aymerich J, Marrades RM, Monsó E, et al. Paradoxical results in the study of risk factors of chronic obstructive pulmonary disease (COPD) re-admission. *Respir Med* 2004;98:851–7.
- van 't Hul AJ, Frouws S, van den Akker E, et al. Decreased physical activity in adults with bronchial asthma. *Respir Med* 2016;114:72–7.
- Bush T, Lovejoy JC, Deprey M, et al. The effect of tobacco cessation on weight gain, obesity, and diabetes risk. *Obesity* 2016;24:1834–41.
- Jain P, Danaei G, Robins JM, et al. Smoking cessation and long-term weight gain in the Framingham heart study: an application of the parametric g-formula for a continuous outcome. *Eur J Epidemiol* 2016;31:1223–9.
- Chaudhuri R, Livingston E, McMahon AD, et al. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003;168:1308–11.
- Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;175:783–90.
- Kane B, Kolsum U, Southworth T, et al. The effects of smoking on the lipopolysaccharide response and glucocorticoid sensitivity of alveolar macrophages of patients with asthma. *Chest* 2009;136:163–70.
- Bourdin A, Adcock I, Berger P, et al. How can we minimise the use of regular oral corticosteroids in asthma? *Eur Respir Rev* 2020;29:190085.
- Bhulani N, Lalani S, Ahmed A, et al. Knowledge of asthma management by general practitioners in Karachi, Pakistan: comparison with international guidelines. *Prim Care Respir J* 2011;20:448–51.
- Lommatzsch M, Sauerbeck IS, Wilmer C, et al. Oral corticosteroid prescription for asthma by general practitioners: a three-year analysis in Germany. *Respir Med* 2021;176:106242.
- Blakey J, Chung LP, McDonald VM, et al. Oral corticosteroids stewardship for asthma in adults and adolescents: a position paper from the thoracic Society of Australia and New Zealand. *Respirology* 2021;26:1112–30.
- MacKinnon M, To T, Ramsey C, et al. Improving detection of work-related asthma: a review of gaps in awareness, reporting and knowledge translation. *Allergy Asthma Clin Immunol* 2020;16:73.
- Coleman T, Murphy E, Cheater F. Factors influencing discussion of smoking between general practitioners and patients who smoke: a qualitative study. *Br J Gen Pract* 2000;50:207–10.
- Houston TK, Scarinci IC, Person SD, et al. Patient smoking cessation advice by health care providers: the role of ethnicity, socioeconomic status, and health. *Am J Public Health* 2005;95:1056–61.

ARTIGO ORIGINAL

Proibição de fumar em espaços fechados a nível nacional e impacto sobre os comportamentos tabágicos e a função pulmonar: uma experiência natural em duas populações

Alexandra Strassmann,¹ Yunus Çolak,^{2,3,4} Miquel Serra-Burriel,¹ Børge G Nordestgaard,^{3,4,5} Alexander Turk,⁶ Shoaib Afzal,^{3,4,5} Milo A Puhan¹

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2021-218436>).

For numbered affiliations see end of article.

Correspondence to

Dr Milo A Puhan, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland; mihoalan.puhan@uzh.ch

AS and YÇ contributed equally. SA and MAP contributed equally.

Received 2 November 2021
Accepted 10 February 2022
Published Online First
11 March 2022

RESUMO

Introdução Muitos países implementaram a proibição de fumar em espaços fechados ao longo das últimas duas décadas. Embora as proibições de fumar tenham mostrado desfechos cardiovasculares reduzidos, pouco se sabe sobre o seu impacto sobre a saúde respiratória. Este estudo investigou o impacto de uma proibição de fumar em espaços fechados a nível nacional sobre os comportamentos tabágicos e a função pulmonar.

Métodos Utilizamos dados transversais repetidos de duas grandes coortes da população geral compostos por 31 807 adultos suíços e 62 093 dinamarqueses. Comparamos associações entre a proibição de fumar e a prevalência do tabagismo e das tendências na função pulmonar pré-broncodilatador na Dinamarca (onde a proibição de fumar em espaços fechados foi introduzida em 2007) e na Suíça (onde a proibição de fumar em espaços fechados foi introduzida em 2010) entre 2005 e 2010 utilizando uma concepção de estudo quase experimental. Realizamos uma análise de diferenças em diferenças com modelos de regressão lineares ajustado para a idade, o sexo, o peso e a altura.

Resultados A Dinamarca apresentou uma maior diminuição dos fumadores ativos quando comparado com a Suíça. Além disso, o volume expiratório forçado no primeiro segundo foi mais elevado nos adultos dinamarqueses do que nos suíços. 26 ml (IC 95%, 2,4 a 49) 1 ano, 88 ml (65 a 112) 2 anos, e 74 ml (51 a 98) 3 anos depois da implementação da proibição de fumar.

Correspondentemente a capacidade vital forçada era mais elevada nos adultos dinamarqueses quando comparada com os adultos suíços [80 ml (50 a 109) após 1 ano e 26 ml (97 a 155) após 2 e 3 anos]. As melhorias foram observadas tanto nos indivíduos que nunca fumaram como nos que continuaram a fumar, sendo mais pronunciadas nos que continuaram a fumar.

Conclusões A proibição de fumar em espaços fechados a nível nacional está associada a uma redução do tabagismo e a uma melhoria da população em geral. Implementar a proibição de fumar em espaços fechados pode melhorar a função pulmonar ao influenciar o comportamento tabágico e reduzir o tabagismo passivo.

INTRODUCTION

Secondhand tobacco smoke is a mixture of smoke from the burning tip of a tobacco product and smoke exhaled by an active smoker.¹ Work and public places such as restaurants, bars and shopping malls have historically been major sources of secondhand smoke exposure. Exposure to secondhand tobacco smoke is linked to several adverse health outcomes such as cardiovascular diseases, lower respiratory tract infections and lung cancer.²⁻⁴ The probability of being exposed to tobacco smoke is high, considering that smoking prevalence was around 20% worldwide and 27% in Europe among people aged 15 years or older in 2015.⁵ Hence, the

Key messages

What is already known on this topic

► Nationwide indoor smoking bans have a beneficial impact on cardiovascular disease and smoking-related mortality, but the impact on respiratory health and smoking prevalence is less clear.

What this study adds

► This study shows that a nationwide indoor smoking ban has a positive impact on lung function and smoking prevalence in the general population, as evidenced by a stronger decrease in active smokers and better lung function in the Danish population up to 3 years after the Danish smoking ban implementation compared with the Swiss population that was not exposed to such a ban within the study period.

How this study might affect research, practice or policy

► This is one of the first quasi-experimental studies in the field of respiratory public health and an example for illustrating key assumptions of the difference-in-difference approach, one of the most commonly used approaches for causal inference when randomised trials are not possible. Our findings can be used as a guidance for policymakers to make evidence-based decisions related to respiratory health in the general population.

vast majority of countries have enacted nationwide indoor smoking bans in the last two decades that prohibit smoking in work and public places. However, the benefits of such bans on public health are difficult to measure. Nonetheless, previous studies have shown that nationwide smoking bans seem to reduce hospital admissions due to cardiovascular disease,^{2,6,7} and countries that have implemented such bans report lower incidence of lung cancer, reduced asthma admission rates and a lower risk of respiratory diseases.^{4,8}

Only few previous studies have shown that exposure to secondhand tobacco smoke is directly linked to lung function with inconsistent result.⁹⁻¹² Most of these studies included hospitality workers as study participants and were based on an uncontrolled before-and-after study design, either with



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Strassmann A, Çolak Y, Serra-Burriel M, et al. *Thorax* doi:10.1136/thoraxjnl-2021-218436

cohort follow-up or repeated cross-sectional surveys.^{13–17} However, temporal trends cannot be controlled in the before-and-after study design that may bias a potential causal relationship between intervention and outcome, but instead a quasi-experimental study design may offer a solution for this.^{18,19} A quasi-experimental study design is an empirical interventional study design that can estimate the impact of a certain intervention in a given population without random assignment, and, hence, shares several advantages with traditional experimental studies and randomised controlled trials.²⁰

In the present study, we investigated the association between nationwide indoor smoking ban and lung function in two general populations using a quasi-experimental study design. We hypothesised that a nationwide indoor smoking ban is associated with less smoking and improved lung function.

METHODS

Study design and populations

We chose a quasi-experimental study design to estimate the impact of a nationwide indoor smoking ban implementation on lung function and smoking behaviour. The quasi-experimental study design compares the exposure-outcome associations between an intervention and a control group, but the group allocation is not randomised. We compared lung function and smoking behaviour trends between Denmark and Switzerland. Denmark introduced a nationwide indoor smoking ban 3 years earlier than Switzerland, thereby providing an ideal framework to approximate the causal relationship by comparing the outcomes of a group exposed to a policy (Denmark) with the outcomes of a group not exposed to the policy (Switzerland). We used repeated cross-sectional data obtained from new independent individuals each year between 2005 and 2010 from two large population-based cohorts to evaluate changes in lung function and smoking behaviour associated with the nationwide indoor smoking ban implementation: the Copenhagen General Population Study and the Swiss LuftiBus Cohort.^{21,22}

Exposure group: Denmark

The Copenhagen General Population Study is a prospective population-based cohort initiated in 2003 with ongoing enrolment. So far, more than 100 000 individuals have been randomly selected and invited from the Danish Civil Registration System to reflect the adult Danish general population. All participants completed a comprehensive questionnaire, underwent a physical examination including spirometry and gave blood for biochemical and genetic

Table 1 Baseline characteristics of the exposed (DK) and control group (CH) averaged over 2005 and 2006 prior to nationwide indoor smoking ban implementation in Denmark

	Exposed group (DK) n=21 045	Control group (CH) n=12 223
Women	10 840 (52)	6372 (52)
Age, mean	61±13	51±17
Smoking status		
Never-smokers	7935 (38)	6402 (52)
Ex-smokers	8337 (40)	2938 (24)
Current smokers	4773 (23)	2876 (24)
Height, cm	171±9.4	170±9.5
Weight, kg	77±15	71±14
FEV ₁ , mL	2840±897	3176±975
FVC, mL	3669±1067	4092±1183

Data are presented as n (%) or mean±SD.

CH, Switzerland; DK, Denmark; FEV₁, forced expiratory volume in first second; FVC, forced vital capacity.

analyses. Additional data for each individual are available through nationwide health registries on hospitalisations and mortality. Individuals participating between 2005 and 2010 were used to form the exposure group. Since Denmark passed the nationwide Smoke-Free Environment Act on 6 June 2007 (Act number 512), which prohibits smoking in indoor workplaces, institutions and schools for children and adults, public places (eg, hotel rooms and public transportation) and hospitality establishments (eg, restaurants and bars), the Copenhagen General Population Study provides appropriate preban and postban spirometry data.²³

Control group: Switzerland

Spirometry data from the control group were derived from the Swiss LuftiBus Cohort. LuftiBus is a health promotion campaign conducted by the Zurich Lung Association in Switzerland, a not-for-profit health organisation.²⁴ The campaign included a bus that travelled throughout Switzerland in the period between 1993 and 2012 providing health information and offering spirometry to the general population. Spirometry data from 85 789 individuals were collected during this time period. Information on smoking, height and weight was also collected during the LuftiBus assessment. Since Switzerland implemented a nationwide indoor smoking ban

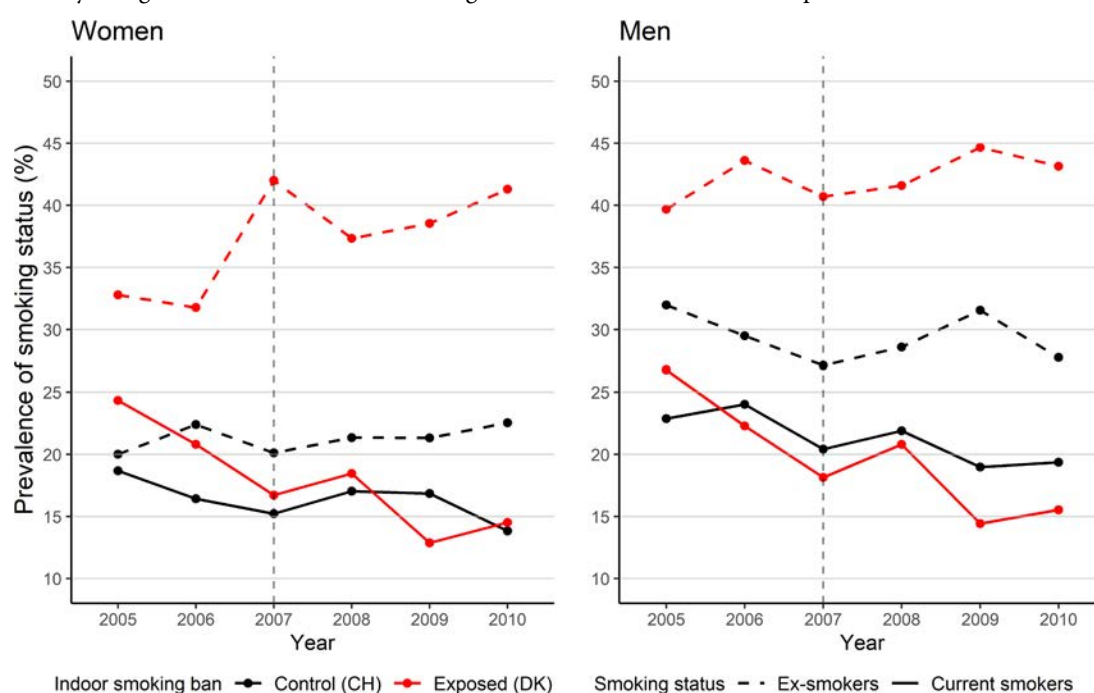


Figure 1 Trends in smoking status between exposed (DK) and control group (CH) from 2005 to 2010. CH, Switzerland; DK, Denmark.

Table 2 Difference-in-difference estimates and 95% CIs for being an ex-, current and never-smoker from 2005 to 2010, stratified by sex (corresponding, online supplemental figure S2–S4)

Year	Probability in Denmark compared with Switzerland in year 2006 Absolute difference in % (95% CI)					
	Ex-smoker		Current smoker		Never-smoker	
	Women	Men	Women	Men	Women	Men
2005	1.4 (–1.3 to 4.0)	–6.2 (–9.1 to –3.3)	1.1 (–1.3 to 3.6)	5.4 (2.6 to 8.1)	–2.4 (–5.5 to 0.6)	0.8 (–2.3 to 3.9)
2006	ref.	ref.	ref.	ref.	ref.	ref.
2007	6.8 (4.0 to 9.6)	0.5 (–2.6 to 3.7)	–5.2 (–7.7 to –2.7)	–2.5 (–5.4 to 0.4)	–1.4 (–4.6 to 1.8)	2.0 (–1.4 to 5.5)
2008	3.3 (0.5 to 6.1)	–1.2 (–4.2 to 1.9)	–3.5 (–6.0 to –1.0)	0.5 (–2.4 to 3.4)	0.3 (–2.9 to 3.5)	0.6 (–2.7 to 3.9)
2009	5.4 (2.5 to 8.2)	–0.3 (–3.4 to 2.8)	–7.8 (–10 to –5.4)	–1.5 (–4.3 to 1.3)	2.6 (–0.7 to 5.8)	1.8 (–1.6 to 5.1)
2010	6.9 (4.1 to 9.8)	2.4 (–0.6 to 5.5)	–3.9 (–6.3 to –1.5)	–1.7 (–4.4 to 1.1)	–3.0 (–6.2 to 0.2)	–0.7 (–4.0 to 2.6)

The estimates in the table show the probability of being an ex-, current or never-smoker in Denmark from 2005 to 2010 in women and men compared with Switzerland in year 2006. For example, the probability of being an ex-smoker was 6.9% higher 3 years after the smoking ban implementation in 2010 for the Danish female population compared with the Swiss female population.

Ref, reference.

on 1 May 2010, ie, 3 years later than Denmark, individuals participating in the LuftiBus between 2005 and 2010 were used to form the control group.

Lung function outcome measurement

Prebronchodilator measurements of forced expiratory volume in the first second (FEV₁) and forced vital capacity (FVC) were used as lung function outcomes in both the Copenhagen General Population Study and the Swiss LuftiBus Cohort. Spirometry was performed with the ndd Medical Technologies EasyOne Spirometer in the Copenhagen General Population Study and the VIASYS SensorMedics Vmax ENCORE 20c in the Swiss LuftiBus Cohort.

In the Copenhagen General Population Study, spirometry use has undergone a rigorous validation process before, including regular calibrations.²⁵ Spirometry was performed in a standing position without the use of a noseclip under strict instructions from a healthcare professional in accordance with the internal standard operating procedures. A valid spirometry performance was based on at least two measurements differing by less than 5%, each with acceptable quality criteria. Only the highest measurement for FEV₁ and FVC was used.

In the Swiss LuftiBus Cohort, technicians calibrated the device daily and were trained at least two times a year. After receiving oral instructions from the technicians, participants performed spirometry while sitting with a straight back and their neck in a neutral position without the use of a noseclip in accordance with the American Thoracic Society/European Respiratory Society recommendations.^{26–27} A minimum of two acceptable measurements out of a maximum of eight were required for a valid spirometry performance. Only the highest measurement for FEV₁ and FVC was used.

Statistical analysis

We compared trends in smoking status between exposed (Denmark) and control (Switzerland) groups in the preban and postban period to identify changes in smoking behaviour. We performed difference-in-difference (DID) analyses to investigate the change in FEV₁ and FVC trends before and after the ban in the exposed group to the change in the outcome in the control group.²⁰ The DID analyses were performed with linear regression models and adjusted for age, sex, weight and height and SEs were clustered at the country level. The DID estimate is the interaction term between time and group in the regression model and can, therefore, be used to compare trends in an outcome over multiple time periods. We also used the probability of being an ex-smoker, current and never-smoker as outcomes in the DID analyses to

assess if smoking ban was associated with an increased smoking cessation rate in the study population.

The year 2006 was the reference year since it immediately preceded the year of policy implementation in Denmark. Outcomes were measured at different time points before and after the ban, and we, therefore, estimated the DID for multiple time points. The main assumption for DID is that of parallel trends in outcomes between exposure and control group before the ban implementation.²⁰ The model assumes that in absence of implementation, the postban trend would have remained unchanged between exposure and control group. Testing for parallel trends before implementation provides evidence of residual confounding over time that would bias the estimates. We provide graphical evidence for fulfilment of this assumption by plotting the mean outcomes by group and time period. We stratified the DID analyses by sex and smoking status rather than including them as covariates in our models to identify modifying effects on the smoking ban and lung function association. Furthermore, we performed subgroup analyses with only never-smokers to investigate if associations are more likely a result of change in smoking behaviour or a reduction of secondhand smoke exposure. To assess the robustness of our results, we used outcomes that should not be affected by the smoking ban policy, that is, height and weight. We chose height as a time-independent and weight as a time-dependent factor since they were available in both cohorts. We studied trends and calculated DID estimates for both outcomes. All statistical analyses were conducted in R V.4.0.4.²⁸

RESULTS

Thirty one thousand eight-hundred and seven participants from Switzerland and 62093 from Denmark aged ≥20 years were enrolled in this study between 2005 and 2010 (online supplemental table S1). At baseline between 2005 to 2006 prior to the nationwide indoor smoking ban implementation in Denmark, Danish individuals were older (61 years vs 51 years), more often ex-smokers (40% vs 24%) and had a lower lung function (FEV₁ 2840 mL and FVC 3669 mL vs FEV₁ 3176 mL and FVC 4092 mL) compared with Swiss individuals (table 1). Otherwise, we found no noteworthy differences. In total, there were 407 missing values (0.4%) in smoking behaviour, these cases had to be excluded from the analyses.

Trends in smoking prevalence

The prevalence of current smokers was decreasing for both countries and sexes between 2005 and 2010 after the nationwide smoking ban implementation (figure 1 and online supplemental

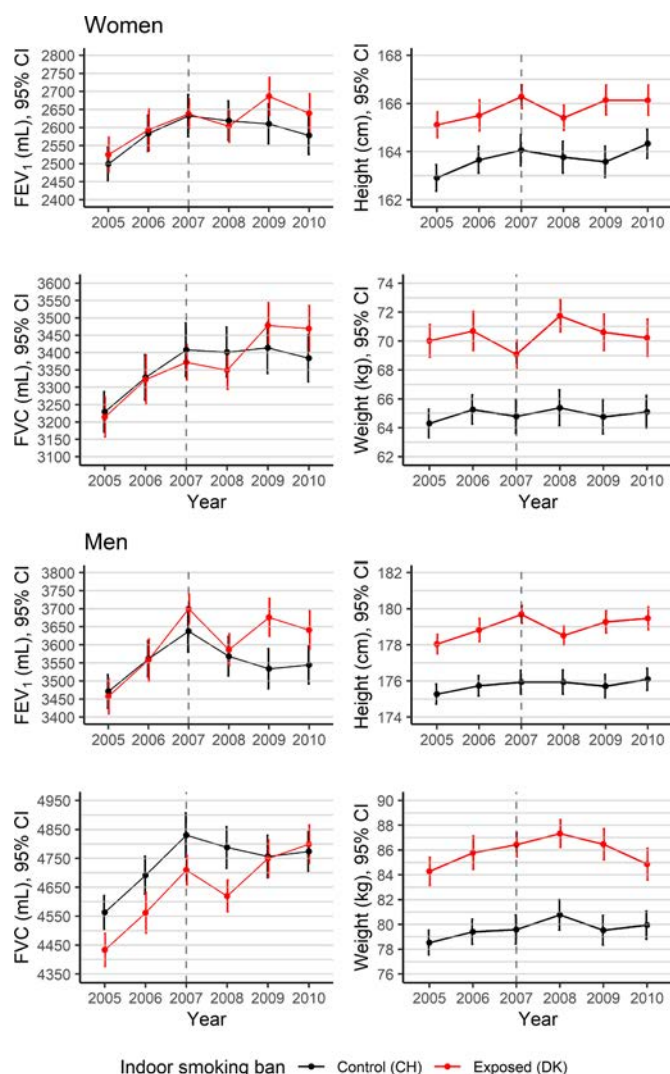


Figure 2 Trends in age-standardised FEV₁, FVC, height, and weight between exposed (DK) and control group (CH) according to sex and 95% confidence intervals (CIs). CH, Switzerland; DK, Denmark; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity.

table S2). The decrease was larger in the exposed group compared with the control group. The prevalence of ex-smokers increased in the female Danish population compared with the female Swiss population. The prevalence of never-smokers was consistently higher in the control than in the exposed group between 2005 and 2010 (online supplemental figure S1 and table S2).

In the DID analyses, we found an increasing probability of being an ex-smoker after the smoking ban implementation in women (table 2 and online supplemental figure S2). Compared with the

reference year 2006, the probability increased to 6.8% (95% CI 4.0 to 9.6) in the year of smoking ban implementation, 3.3% (0.5 to 6.1) after 1 year, 5.4% (2.5 to 8.2) after 2 and 6.9% (4.1 to 9.8) after 3 years in the exposed group. We did not observe a similar increase in male participants.

Accordingly, the probability of being a current smoker decreased in the female but not in the male population by −5.2% (95% CI −7.7 to −2.7) in the year of smoking ban implementation, −3.5% (−6.1 to −1.0) after 1 year, −7.8% (−10 to −5.4) after 2 and −3.9% (−6.3 to −1.5) after 3 years in the exposed group compared with the reference year 2006 (table 2 and online supplemental figure S3). The probability of being a never-smoker did not change after the smoking ban implementation between the two populations (table 2 and online supplemental figure S4).

Trends in lung function

Trends in FEV₁ and FVC were almost parallel between the exposed and control group in the preban period from 2005 to 2007 (figure 2 and online supplemental table S3). We observed changes in trends with implementation of the nationwide smoking ban from 2007 and onwards. As expected, trends in height and weight were parallel in the preban and postban period, and the 95% CIs did not overlap in any of the years between the two groups.

Compared with the control group, FEV₁ in the exposed group was higher: 26 mL (95% CI 2.4 to 49) after 1 year, 88 mL (65 to 112) after 2 years and 74 mL (51 to 98) after 3 years of smoking ban implementation (figure 3 and online supplemental table S4). Correspondingly, FVC was also higher: 80 mL (50 to 109) after 2 years and 126 mL (97 to 155) after 3 years of smoking ban implementation.

Subgroup analyses

For never-smokers, FEV₁ was highest with 65 mL (95% CI 33 to 97) after 2 years and remained constant after 3 years of smoking ban implementation (figure 4 and online supplemental table S5). FVC changed from 66 mL (26 to 106) after 2 years to 99 mL (59 to 139) after 3 years. The DID estimate was higher for current and ex-smokers than for never-smokers but with overlapping CIs (figure 4 and online supplemental table S5). FEV₁ was 97 mL (62 to 132) after 2 years and FVC 143 mL (101 to 186) after 3 years in current and ex-smokers. For women, FEV₁ and FVC were highest 3 years after smoking ban implementation with 81 mL (95% CI 55 to 108) and 133 mL (99 to 166), respectively (online supplemental figure S5 and table S6). For men, FEV₁ was highest 2 years and FVC 3 years after smoking ban implementation with 112 mL (73 to 151) and 110 mL (64 to 157), respectively.

Sensitivity analyses

As expected, we could not see a clear pattern for change in height and weight between exposed and control group after nationwide smoking ban implementation. Height changed by −0.3 cm (95% CI −0.6 to −0.002) after 1 year, 0.5 cm (0.2 to 0.8) after 2 years and

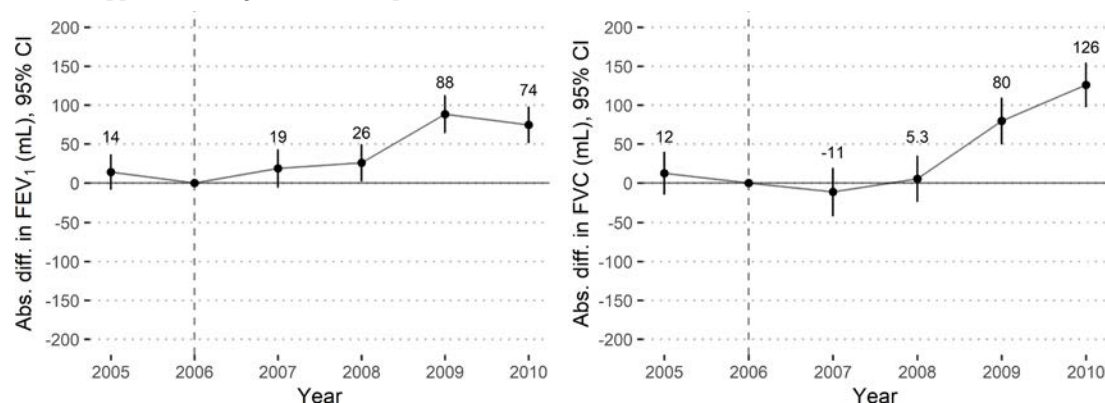


Figure 3 Age-standardised difference-in-difference for FEV₁ and FVC from 2005 to 2010 and 95% CIs. The dotted line represents the reference year: 1 year prior the smoking ban implementation in the exposed group. Analyses were adjusted for age, sex, weight, and height and standard errors were clustered at the country level. Abs. diff., absolute difference; FEV₁, forced expiratory volume in first second; FVC, forced vital capacity.

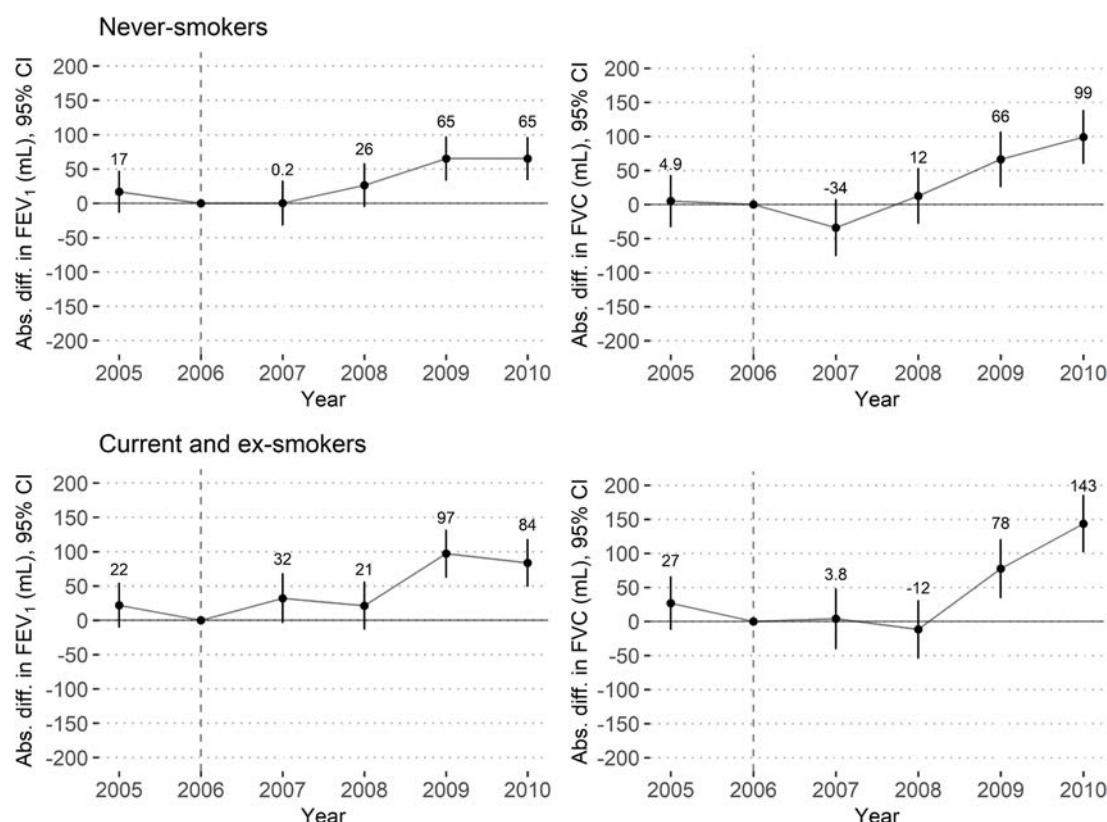


Figure 4 Age-standardised difference-in-differences estimates for FEV₁ and FVC from 2005 to 2010 among never- and ever-smokers and 95% CIs. The dotted line represents the reference year: 1 year prior the smoking ban implementation in the exposed group. Analyses were adjusted for age, sex, weight, and height and standard errors were clustered at the country level. Abs. diff., absolute difference; FEV₁, forced expiratory volume in first second; FVC, forced vital capacity.

0.1 cm (−0.2 to 0.4) after 3 years of implementation in the exposed group (online supplemental figure S6 and table S7). Correspondingly, weight changed by 1.0 kg (0.4 to 1.5), 0.6 kg (−0.02 to 1.1) and −0.7 kg (−1.2 to −0.1), respectively.

DISCUSSION

In this two-population natural experiment, we found that population FEV₁ and FVC increased in Denmark, the country that implemented a nationwide indoor smoking ban compared with Switzerland that did not. FEV₁ and FVC were also increased in the subpopulation of never-smokers, indicating an improved lung function through reduced secondhand smoke exposure. Since FEV₁ and FVC differences tended to be even larger for ex-smokers and current smokers than for never-smokers, our findings suggest both a direct impact through smoking cessation and an indirect impact through reduced secondhand smoke exposure. The probability of being an ex-smoker increased and the probability of being a current smoker decreased in Denmark in the year of the ban implementation and thereafter in women but not in men. This is one of the first studies to provide evidence for a positive association between indoor smoking ban and respiratory health in the general population using a quasi-experimental approach.

Mechanistically, the improved lung function in ex-smokers and current smokers is likely explained in part by the observed increased smoking cessation in exposed versus control population. However, the subgroup analyses within never-smokers indicate that changes in lung function may not be due to changes in smoking behaviour (eg, smoking cessation) but rather due to a reduced exposure to secondhand smoke. A positive influence of reduced exposure to secondhand smoke likely will affect both never-smokers and ever-smokers.

Two systematic reviews have shown that evidence for an association between indoor smoking ban and lung function is scarce and inconsistent. In a Cochrane Review from 2016, two out of four studies reported improved lung function after an indoor smoking ban^{11 15 29}; however, all four studies were based on an uncontrolled

before-and-after study design and included small samples of hospitality workers (n ranging from 71 to 105). In another systematic review from 2017, eight out of nine studies were based on small samples of hospitality workers (n ranging from 53 to 198) and one study was based on healthy miners.¹² Six out of these nine studies reported positive effects of smoking bans on lung function: the pooled meta-analysis resulted in a net difference in FEV₁ of 100 mL (95% CI −40 to 240) (three studies included) and in FVC of 190 mL (130 to 250) (two studies included). Based on these systematic reviews and our extensive literature search, we could not find any study that estimated the association of indoor smoking ban on lung function based on the general population and using a quasi-experimental study design.

We found that the mean difference in FEV₁ was 88 mL higher after 2 years and in FVC 126 mL after 3 years of smoking ban implementation. These changes may have significant repercussions for public health as several large observational studies have shown a strong association of lung function with mortality in community-based cohorts.^{30 31} In a prospective, international, community-based cohort study including 126 359 adults, the largest population burden was associated with mildly to moderately reduced FEV₁.³⁰ Therefore, even a reduction of mildly to moderately impaired FEV₁ may have a great impact on health, in particular, on mortality and cardiovascular diseases.³⁰

Our study has several limitations. One could argue that a potential limitation is that there was no random allocation of study participants to the exposed or control group. However, such an experiment would be unethical as smoking is known to be harmful. Thus, the best approach is to use a quasi-experimental study design to derive potential causal relationships. As our assumptions were met and results seemed robust, we believe our results to be valid. Another potential limitation is that there were no longitudinal lung function data available, which would have allowed a pre-post comparison within the same individuals. However, the DID method considers changes over time within a group as well as relative to a control group. Although the Danish and the Swiss

cohorts are similar in terms of key characteristics, we cannot fully rule out that other important cohort differences, such as comorbidities, may have confounded our study results.

The quasi-experimental study design is the major strength of this study. The comparison with an appropriate control group provides suggestive evidence for a causal relationship between smoking ban and lung function changes. The risk that changes in outcomes are a result of natural temporal trends or unmeasured events that occurred in the same time period is minimised in controlled study designs compared with the uncontrolled before-and-after study design. The greatest challenge of DID analyses is finding an appropriate control group that meets the parallel trend assumption. We show that trends in outcomes were almost parallel in the preban period and that our findings were unlikely to be a result of unobserved trends. We presented DID estimates at multiple time points, which allows the effect to be described up to 3 years after the smoking ban implementation. In the sensitivity analyses, we showed that other outcomes (ie, height and weight) were unaffected by the smoking ban implementation, which supports the assumption that changes in lung function were a result of the smoking ban. Results from quasi-experiments have higher external validity than those from traditional experimental studies because the inclusion of participants is less restrictive.¹⁸ Therefore, we are confident to say that the results of this study likely can be generalised to a general population with similar exposure patterns.

In conclusion, we found that nationwide indoor smoking ban is associated with less smoking and improved lung function in the general population. Implementing an indoor smoking ban can improve lung function by influencing smoking behaviour and reducing secondhand smoke.

Author affiliations

¹Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland

²Department of Respiratory Medicine, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark

³The Copenhagen General Population Study, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark

⁴Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

⁵Department of Clinical Biochemistry, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark

⁶See-Spital Horgen, Horgen, Switzerland

Contributors SA and MAP had full access to all data in the study and had final responsibility for the decision to submit for publication. Study concept and design: AS, YÇ, MSB, BGN, AT, SA and MAP. AT provided data of the LuftiBus Cohort. Statistical analyses: SA, MSB, AS. Interpretation of the data: AS, YÇ, MSB, BGN, SA and MAP. Drafting the manuscript: AS and YÇ. Revision of the manuscript for important intellectual content: AS, YÇ, MSB, BGN, AT, SA, AT and MAP. MAP is responsible for the overall content as guarantor.

Funding Supported by the Swiss National Science Foundation (grant 32 473B_173043), Zurich Lung Association (no grant number) and Herlev and Gentofte Hospital (no grant number).

Disclaimer The funders had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Competing interests YÇ reports personal fees from Boehringer Ingelheim, AstraZeneca, and Sanofi Genzyme outside of the submitted work. MSB reports grants from the European Commission's H2020 and EIT Health programmes outside of the submitted work.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Herlev and Gentofte Hospital and a Danish ethical committee (approval number: H-KF-01-144/01) and the Ethics Committee of the Canton of Zurich in Switzerland (BASEC-Nr. 2017-01804). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The Swiss data are available from the corresponding author MAP (miloalan.puhan@uzh.ch) upon reasonable request. The Danish data are available from SA (shoaib.afzal@regionh.dk) upon reasonable request. However, according to national Danish laws, only summary-level data (as reported herein) and scripts can be shared.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Shoaib Afzal <http://orcid.org/0000-0002-1442-4694>

REFERENCES

- International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans 100E: a review of human carcinogens 2012.
- Callinan JE, Clarke A, Doherty K, et al. Legislative smoking bans for reducing secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev* 2010;CD005992.
- Eisner MD, Balmes J, Katz PP, et al. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. *Environ Health* 2005;4:7.
- Du Y, Cui X, Sidorovskov G, et al. Lung cancer occurrence attributable to passive smoking among never smokers in China: a systematic review and meta-analysis. *Transl Lung Cancer Res* 2020;9:204–17.
- World Health Organization. WHO global report on trends in prevalence of tobacco use 2000–2025, third edition, 2019. Available: <https://www.who.int/publications/i/item/who-global-report-on-trends-in-prevalence-of-tobacco-use-2000-2025-third-edition> [Accessed 29 Dec 2021].
- Mackay DF, Irfan MO, Haw S, et al. Meta-analysis of the effect of comprehensive smoke-free legislation on acute coronary events. *Heart* 2010;96:1525–30.
- Pell JP, Haw S, Cobbe S, et al. Smoke-free legislation and hospitalizations for acute coronary syndrome. *N Engl J Med* 2008;359:482–91.
- Tan CE, Glantz SA. Association between smoke-free legislation and hospitalizations for cardiac, cerebrovascular, and respiratory diseases: a meta-analysis. *Circulation* 2012;126:2177–83.
- Eisner MD, Wang Y, Haight TJ, et al. Secondhand smoke exposure, pulmonary function, and cardiovascular mortality. *Ann Epidemiol* 2007;17:364–73.
- Lai H-K, Hedley AJ, Repace J, et al. Lung function and exposure to workplace second-hand smoke during exemptions from smoking ban legislation: an exposure-response relationship based on indoor PM_{2.5} and urinary cotinine levels. *Thorax* 2011;66:615–23.
- Frazer K, Callinan JE, McHugh J, et al. Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev* 2016;2:CD005992.
- Rando-Matos Y, Pons-Vigués M, López MJ, et al. Smokefree legislation effects on respiratory and sensory disorders: a systematic review and meta-analysis. *PLoS One* 2017;12:e0181035.
- Eisner MD, Smith AK, Blanc PD. Bartenders' respiratory health after establishment of smoke-free bars and taverns. *JAMA* 1998;280:1909–14.
- Larsson M, Boëthius G, Axelsson S, et al. Exposure to environmental tobacco smoke and health effects among hospitality workers in Sweden—before and after the implementation of a smoke-free law. *Scand J Work Environ Health* 2008;34:267–77.
- Goodman P, Agnew M, McCaffrey M, et al. Effects of the Irish smoking ban on respiratory health of bar workers and air quality in Dublin pubs. *Am J Respir Crit Care Med* 2007;175:840–5.
- Rajkumar S, Stolz D, Hammer J, et al. Effect of a smoking ban on respiratory health in nonsmoking hospitality workers: a prospective cohort study. *J Occup Environ Med* 2014;56:e86–91.
- Faber T, Mizani MA, Sheikh A, et al. Respiratory symptoms, pulmonary function, and markers of inflammation among bar workers before and after a legislative ban on smoking in public places. *JAMA* 2006;296:1742–8.
- Maciejewski ML. Quasi-experimental design. *Biostat Epidemiol* 2020;4:38–47.
- Faber T, Mizani MA, Sheikh A, et al. Investigating the effect of England's smoke-free private vehicle regulation on changes in tobacco smoke exposure and respiratory disease in children: a quasi-experimental study. *Lancet Public Heal* 2019;4:e607–17.
- Wing C, Simon K, Bello-Gomez RA. Designing difference in difference studies: best practices for public health policy research. *Annu Rev Public Health* 2018;39:453–69.
- West EA, Strassmann A, Wang C, et al. Increase in airway obstruction between 1993 and 2012 in Switzerland. An observational study. *Ann Am Thorac Soc* 2020;17:457–65.
- Çolak Y, Afzal S, Nordestgaard BG, et al. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. *Lancet Respir Med* 2017;5:426–34.
- Ministry of the Interior and Health Denmark. Smoke-free environment acts, 2007. Available: <https://www.tobaccocontrol.org/files/live/Denmark/Denmark-ActNo.512.pdf> [Accessed 16 Dec 2020].
- Zurich Lung Association. LuftiBus, 2020. Available: <https://www.lunge-zuerich.ch/de/projekte/luftibus> [Accessed 25 May 2020].
- Lökke A, Marott JL, Mortensen J, et al. New Danish reference values for spirometry. *Clin Respir J* 2013;7:153–67.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *American thoracic Society. Am Rev Respir Dis* 1991;144:1202–18.
- R Core Team. R: a language and environment for statistical computing. R foundation for statistical computing, 2021. Available: <https://www.r-project.org/>
- Durham A-D, Bergier S, Morisod X, et al. Improved health of hospitality workers after a Swiss cantonal smoking ban. *Swiss Med Wkly* 2011;141:w13317.
- Duong M, Islam S, Rangarajan S, et al. Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV1 (PURE): an international, community-based cohort study. *Lancet Glob Health* 2019;7:e613–23.
- Schünemann HJ, Dorn J, Grant BJ, et al. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the buffalo health study. *Chest* 2000;118:656–64.

ARTIGO ORIGINAL

Obstrução do fluxo de ar e disfunção das pequenas vias respiratórias na sequência de uma tuberculose pulmonar: um inquérito transversal

Zhenzhen Xing,^{1,2} Tieying Sun,¹ Jean-Paul Janssens,³ Di Chai,¹ Weiming Liu,⁴ Yaqi Tong,¹ Yuxia Wang,¹ Yali Ma,¹ Mingming Pan,¹ Jia Cui,¹ Chen Wang,^{5,6,7,8} YanFei Guo¹

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2021-218345>).

For numbered affiliations see end of article.

Correspondence to

Dr YanFei Guo, Department of Respiratory and Critical Care Medicine; National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Hospital, Beijing, Beijing, China; yanfeigu2003@126.com

ZX and TS contributed equally.

Received 12 October 2021

Accepted 8 March 2022

Published Online First

31 March 2022



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Xing Z, Sun T, Janssens J-P, et al. *Thorax* doi:10.1136/thoraxjnl-2021-218345

RESUMO

Objetivos Insuficiência da função pulmonar e sintomas respiratórios crônicos depois da tuberculose são relativamente comuns em países de rendimento médio e baixo. Procuramos estimar o impacto da pós-tuberculose (pós-TB) na função pulmonar.

Métodos Este grande estudo transversal populacional incluiu sujeitos com 15 ou mais anos de idade com medições de espirometria pós-broncodilatador tecnicamente aceitáveis. A pós-TB foi diagnosticada com base em provas radiológicas e/ou histórico médico. A obstrução do fluxo de ar foi definida como uma relação entre volume expiratório forçado pós-broncodilatador em 1 seg/capacidade vital forçada abaixo do limiar mais baixo do resultado normal das equações de função pulmonar da Global Lung Function Initiative (GLI). A disfunção das pequenas vias respiratórias foi diagnosticada quando dois dos indicadores seguintes se encontravam abaixo de 65% do previsto: fluxo expiratório médio máximo, fluxo expiratório forçado (FEF) 50% ou FEF 75%.

Resultados Nesta amostra da população (N=8680, média de idade: 40,1 anos), 610 [7,0% (IC 95%, 6,5 a 7,6)] participantes eram pós-TB. Os sujeitos pós-TB apresentavam sintomas respiratórios mais frequentes (46,8% vs 28,3%). Entre os sujeitos pós-TB, 130 [21,3% (IC 95%, 18,1 a 24,8)] apresentavam obstrução do fluxo de ar; OR da obstrução do fluxo de ar estava significativamente associada ao pós-TB depois do ajuste para fatores de confusão (OR 1,31, IC 95%, 1,05 a 1,62). A pós-TB também estava associada a uma disfunção das vias respiratórias pequenas (OR 1,28, IC 95%, 1,07 a 1,53), que estava presente em 297 [48,9% (IC 95%, 33,9 a 53,0)] sujeitos pós-TB.

Conclusões As nossas conclusões apoiam o conhecimento já existente de que o pós-TB está positivamente associado a insuficiência da função pulmonar e proporcionam sintomas respiratórios frequentes. O pós-TB deve ser considerado uma causa potencialmente importante na obstrução das vias respiratórias e nos sintomas respiratórios em pacientes originários de países com uma elevada carga de tuberculose.

INTRODUCTION

Tuberculosis (TB) is a major global health problem especially in low-income and middle-income countries; it is among the top 10 causes of death and the leading cause from a single infectious agent. An estimated 10.0 million people developed TB worldwide, leading to an estimated 1.3 million TB deaths among HIV-negative people in 2020.¹ China is the third contributor to this worldwide epidemic and accounts for 8.4% of all cases, after India (26%) and Indonesia (8.5%).² While treatment is available and efficient in non-multidrug-resistant/extensively drug-resistant (MDR/XDR) cases, microbiological cure may not prevent long-term pulmonary complications of TB.

Key messages

What is already known on this topic

- Several publications have reported the prevalence of post-tuberculosis (post-TB) sequelae, but the definition of post-TB and studied population are inconsistent. We wished estimate the prevalence of post-TB in low-income areas in China and identify the impact of post-TB on pulmonary function.

What this study adds

- Our findings confirmed that post-TB is highly prevalent, is positively associated with airflow obstruction and associated with a high frequency of respiratory symptoms.

How this study might affect research, practice or policy

- Better understanding and addressing airflow obstruction and respiratory symptoms after TB is needed; this is most relevant in low-resource, high-burden settings, where healthcare resources and diagnostics means are limited.

While smoking remains the key risk factor for chronic obstructive pulmonary disease (COPD), a considerable burden of the disease in low-income and middle-income countries cannot be explained by smoking alone. TB and other non-smoking risk factors of COPD such as domestic pollution are of increasing importance.³⁻⁶ An association between past TB and airflow obstruction, characteristic of COPD, has been reported in large population-based epidemiological studies.⁷⁻¹⁰ However, most of these studies included subjects above 40 years of age and are limited to low TB burden regions. There is also some evidence that pulmonary TB is related to persistent symptoms and has a substantial adverse impact on quality of life. A high burden of self-reported symptoms after TB treatment completion has been reported.¹¹⁻¹³ Better understanding and addressing of airflow obstruction and respiratory symptoms after TB is needed: this is most relevant in low-resource, high-burden settings, where healthcare resources and diagnostic modalities are limited.

In this study, we aimed to describe the general characteristics, pulmonary function parameters and chronic respiratory symptoms of people with

post-TB. We also quantified the association between post-TB status and chronic respiratory symptoms and further characterised the relationship between post-TB and pulmonary function impairment.

METHODS

Study design and participants

The present study, conducted in Tibet and Xinjiang Uygur Autonomous Regions, analysed pulmonary health in long-term residents of these areas aged 15 years or older, details of which have been reported elsewhere.¹⁴ A multistage stratified sampling procedure was used to select subjects from 13 local regions between June 2015 and August 2016. The proportion of samples from each gender and age group was based on the 2010 census of the Chinese population. A standardised questionnaire covering sociodemographic status, living conditions, respiratory symptoms, history of respiratory diseases and comorbidities, environmental and occupational factors was administered by experienced interviewers at local community health centres. Furthermore, a range of physical measurements were undertaken using a standard protocol, including anthropometry, blood pressure, oxygen saturation by pulse oximetry (SpO_2) and lung function. A posterior–anterior chest radiograph was obtained during deep inspiration in a standing position using a radiography unit.

Procedures

Pulmonary function tests were measured by trained technicians in all qualified study participants (spirometry) with a Master-Screen™ Pneumo PC spirometer (CareFusion, Yorba Linda, California) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations by trained technicians.¹⁵ The spirometer was calibrated daily using a 3-litre syringe to ensure measured volumes within 3% of syringe volume, before data collection; ambient temperature, humidity and altitude were also recorded daily. Each participant underwent the same procedure two times, before and after receiving a bronchodilator (BD) (400 µg of salbutamol through a 500 mL spacer). The forced expiratory manoeuvres were performed 3–8 times until the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were reproducible within 150 mL.¹⁶ Acceptability of FVC and FEV_1 was scored using an A to F grading system. Performing three acceptable manoeuvres with an FVC variability of 100 mL or less was rated 'A'; a variability of 100–150 mL was rated 'B'; variability between 150 and 200 mL was scored 'C'. A, B or C grades were considered acceptable for analysis. Data were uploaded daily to a database, examined for incoherent data by the study supervisors and by the principal investigator. Quality control, based on the American Thoracic Society/European Respiratory Society criteria, was performed by a field supervisor at the filing centre, and included analysis of flow volume curves for artefacts and appropriate technique. Airflow obstruction was defined as a post-BD FEV_1/FVC ratio below the lower limit of normal (LLN) for height, age and sex, based on the reference values from the Global Lung Function Initiative (GLI) lung function equations for a North East Asian population.¹⁷ A post-BD FEV_1/FVC ratio of <0.70 was also used to define airflow obstruction in a sensitivity analysis based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.¹⁸ Spirometric restriction was defined as a post-BD FVC ratio below the LLN for the height, age and sex based on the same reference population with a normal FEV_1/FVC ratio. We used three indicators of lung function to assess small airway dysfunction, namely, maximal mid-expiratory flow (MMEF), forced expiratory flow (FEF) at 50% of vital capacity and FEF at 75% of vital capacity. Small airway dysfunction was diagnosed when at least two of these three indicators were below 65% of predicted values.¹⁹

Post-TB was defined as having highly suggestive images of pulmonary TB sequelae on chest radiographs and/or a positive medical history of TB.^{7–9} The diagnosis of post-TB lesions was considered in the presence of discrete linear or reticular fibrotic scars or dense nodules with distinct margins, with or without calcifications, within the upper lobes.²⁰ The radiographs were reviewed

by two experienced radiologists who were blinded to the details of the participants, using standard criteria for reporting radiologic abnormalities.²¹ Discordant findings were resolved by discussion and consensus. A medical history of tuberculosis was defined as a positive answer to the question 'Has a doctor or other healthcare provider ever told you that you had tuberculosis?'.

Definitions of ever smoker, never smoker, household air pollution (HAP), occupational exposure have been previously reported.¹⁴ Self-reported history of physician-diagnosed hypertension, chronic cardiovascular disease of any cause, diabetes mellitus, dyslipidaemia and asthma was also obtained. We defined the chronic respiratory symptoms by their persistence for at least 3 consecutive months during a year based on questionnaires.

Statistical analysis

All analyses were performed with R statistical programme V.4.0.3 (www.r-project.org/). The analyses included a description of the sample, evaluation of mean spirometric results, calculation of the prevalence of airflow obstruction and small airway dysfunction according to history of post-TB. Statistical significance of differences was tested by analysis of variance (ANOVA) or Student's *t* test for continuous variables and by χ^2 test for categorical variables. Logistic regression models were built to quantify the relationship between post-TB and airflow obstruction. Potential confounders considered were: age, sex, region, educational level, smoking history and pack-years, HAP, occupational exposure and history of asthma. ORs with 95% CIs were determined for three models. Differences with two-sided $p < 0.05$ were considered statistically significant.

RESULTS

Of the 12 991 subjects invited to participate, 11 747 completed the survey questionnaire and performed chest X-rays. Among them, 2503 participants were excluded from this analysis because they could not complete post-BD testing. After excluding 564 participants without reliable spirometric data, the final study sample included 8680 participants (4407 (50.8%) women, 4273 (49.2%) men), with an overall mean age of 40.1 (SD 15.3) years (online supplemental figure E1).

Among the 8680 participants, 610 (7.0%) had evidence of post-TB (table 1). Number of post-TB subjects, as defined by evidence of post-TB on chest radiographs only, was 463 (5.3% (95% CI 4.9% to 5.8%)), while that based on self-reported history of TB only was 98 (1.1% (95% CI 0.9% to 1.4%)). There were 49 (0.6% (95% CI 0.4 to 0.7%)) subjects for whom there was both evidence of post-TB on chest radiographs and a history of TB. Post-TB individuals were more likely to be men, older, ever smokers, city dwellers and have a lower educational level. They reported more comorbidities and had lower oxygen saturation (SpO_2). They had a higher frequency of chronic cough, sputum, recurrent wheezing and dyspnoea in daily life when compared with those without 'post-TB'. Also, they reported a higher rate of at least one of the listed respiratory symptoms (46.8% vs 28.3%). Spirometric indices: when compared with subjects without 'post-TB', post-TB participants had lower post-BD values for $\text{FEV}_1/\text{FVC}\%$ (mean (SD): 78.4 (12.2) vs 82.4 (10.7), $p < 0.001$), FVC (3.57 (1.02) vs 3.73 (0.96), $p < 0.001$) and FEV_1 (2.80 (0.91) vs 3.07 (0.85), $p < 0.001$) and lower MMEF, FEF_{50} and FEF_{75} values as % of predicted. Older age, being a city dweller, having a history of asthma and suffering from airflow obstruction significantly increased probability of having a post-TB status, while higher educational level was related with a lower risk (figure 1).

Overall prevalence of airflow obstruction in post-TB subjects (21.3% (95% CI 18.1% to 24.8%)) was significantly higher than in 'non-post-TB' subjects (15.2% (95% CI 14.5% to 16.0%)). This was also the case for small airway dysfunction (48.9% (297 of 607) vs 37.5% (2993 of 7987)). Standardised prevalence of these conditions increased steadily with age ($p < 0.001$ for airflow obstruction and small airway dysfunction) (figure 2). Using the GOLD threshold of a fixed FEV_1/FVC ratio < 0.7 , prevalence of airflow obstruction in post-TB subjects (all: 19.3% (95% CI 16.2 to 22.4); men: 22.3%

Table 1 Characteristics of participants according to history of post-TB

Variables	Post-TB (n=610)	Non post-TB (n=8070)	P value
Male	328 (53.8%)	3945 (48.9%)	0.022
Age, years	49.31 (15.21)	39.49 (15.17)	<0.001
City dweller	256 (42.1%)	2580 (32.1%)	<0.001
Education level			
Primary school and lower	362 (59.4%)	3512 (43.5%)	<0.001
Middle and high school	180 (29.5%)	3225 (40.0%)	
College and higher	68 (11.1%)	1333 (16.5%)	
Smoking status			
Never smoker	405 (66.4%)	5866 (72.7%)	<0.001
Ever smoker	205 (33.6%)	2201 (27.3%)	
Comorbidities			
Hypertension	97 (16.3%)	636 (8.0%)	<0.001
Chronic cardiovascular disease	11 (1.8%)	66 (0.8%)	0.022
Diabetes mellitus	14 (2.7%)	128 (2.1%)	0.303
Dyslipidaemia	70 (13.4%)	478 (7.9%)	<0.001
History of asthma	32 (5.3%)	118 (1.5%)	<0.001
Respiratory symptoms			
Frequent cough	109 (18.0%)	757 (9.5%)	<0.001
Sputum	110 (18.2%)	750 (9.4%)	<0.001
Recurrent wheezing	54 (8.9%)	310 (3.9%)	<0.001
Dyspnoea in daily life	198 (32.7%)	1570 (19.6%)	<0.001
At least one of the symptoms	284 (46.8%)	2259 (28.3%)	<0.001
Lung function parameters			
FVC post-BD, L	3.57 (1.02)	3.73 (0.96)	<0.001
FVC post-BD % pred	106.20 (25.55)	104.19 (22.33)	0.060
FEV ₁ post-BD, L	2.80 (0.91)	3.07 (0.85)	<0.001
FEV ₁ post-BD % pred	100.55 (28.49)	101.47 (23.60)	0.437
FEV ₁ /FVC post-BD, %	78.40 (12.18)	82.38 (10.72)	<0.001
MMEF post-BD % pred	68.95 (35.07)	78.90 (57.69)	<0.001
FEF _{50%} post-BD % pred	83.52 (36.17)	88.48 (31.06)	0.001
FEF _{75%} post-BD % pred	85.01 (58.02)	92.33 (47.12)	0.003
Oxyhemoglobin saturation (SpO ₂), %	91.39 (6.39)	93.45 (5.25)	<0.0001

Data are expressed as number (%) or mean (SD).

FEF, forced expiratory flow; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; post-BD, post-bronchodilator.

(95% CI 17.8 to 26.8); women: 16.0% (95% CI 11.7 to 20.3)) was also significantly higher than in 'non-post-TB' participants (all: 10.9% (95% CI 10.2 to 11.6); men: 12.2% (95% CI 11.2 to 13.2); women: 9.6% (95% CI 8.7 to 10.5)) (figure 3).

Table 2 presents the characteristics and spirometric results of participants according to post-TB and airflow obstruction status. Subjects with airflow obstruction and a history of post-TB had lower post-BD spirometric values, a higher proportion of GOLD III-IV stages (online supplemental figure E2), more respiratory symptoms, a more frequent history of asthma, a lower SpO₂ and a higher percentage of subjects with a chronic obstructive pulmonary disease assessment test (CAT) score ≥ 10 compared with 'non-post-TB' participants. Importantly, post-TB subjects without airflow obstruction actually reported more respiratory symptoms (46.0% vs 29.5%, $p < 0.001$) and had a lower SpO₂ (91.0% (0.2) vs 94.4% (0.1), $p < 0.001$) and a lower FVC (absolute value and % predicted) than 'non-post-TB' subjects with airflow obstruction.

Subjects with a restrictive pattern: online supplemental table E1 shows the demographic characteristics of participants according

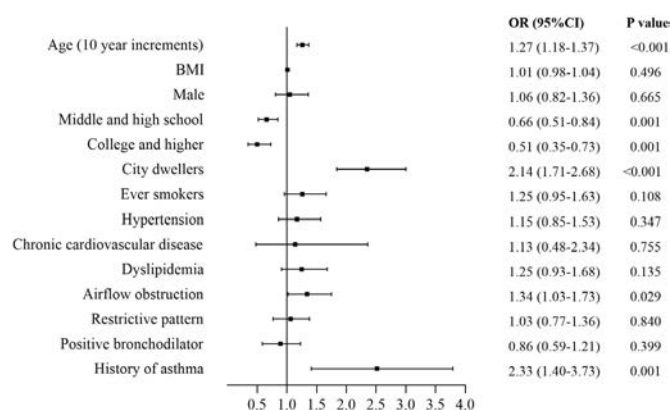


Figure 1 Forest plot showing OR for post-TB participants. Each square represents an OR. The horizontal lines indicate 95% CIs. BMI, body mass index; TB, tuberculosis.

to their lung function (presence of a restrictive pattern vs normal) and post-TB status. Post-TB participants with normal spirometry had nearly two times as much respiratory symptoms as those without a history of post-TB and had lower pre-BD and post-BD (% predicted) FEV₁/FVC% and MMEF. Post-TB subjects with a restrictive pattern had more respiratory symptoms, lower SpO₂ and more severe lung function indices. Prevalence of airflow obstruction, restrictive pattern and small airway dysfunction according to post-TB status is shown in online supplemental figure E3.

When compared with 'non-post-TB' participants, having a post-TB status was associated with an OR (95% CI) of 1.31 (1.05 to 1.62) for airflow obstruction and of 1.28 (1.07 to 1.53) for small airway dysfunction after adjusting for gender, age, region, education, smoking status, exposure to HAP, occupation and history of asthma. In a subgroup analysis, being a post-TB never smoker was independently associated with airflow obstruction (1.37 (1.04 to 1.78], $p = 0.023$) and (1.47 (1.18 to 1.83), $p < 0.001$) small airway dysfunction after adjusting for above-mentioned variables (table 3). The effect sizes for potential confounders are provided in online supplemental tables E2 and E3. Post-TB was significantly associated with respiratory symptoms after adjusting for gender, age, region and education, smoking status, exposure to HAP and occupation (online supplemental table E4).

DISCUSSION

To the best of our knowledge, this is the first study with a rigorous sampling design to estimate the burden of post-TB and assess the association with chronic airflow obstruction and respiratory symptoms in China. Our findings suggest that socioeconomic status, respiratory symptoms, comorbidities and lung function parameters were worse in participants who had post-TB compared with 'non post-TB' participants, and even worse in those with post-TB and airflow obstruction. Our data show that 7.0% of residents had post-TB: in this group, 21.3% had airflow obstruction and 48.9% small airway dysfunction. Post-TB was associated with an increased odds of airflow obstruction and small airway dysfunction after adjustment for confounding factors. The magnitude of the OR between TB and airflow obstruction was much higher among never smokers, which suggests that post-TB may be a major risk factor per se especially among never smokers. We also filled in the age gap by providing data for subjects aged below 40 years old, since most previous reports of an association between airflow obstruction and post-TB included subjects aged over 40.^{6 8-10}

Prior publications have reported the prevalence of post-TB sequelae, but the related burden remains undetermined.^{8-10 22 23} The reasons may be inconsistency in definition, heterogeneity of populations studied and a lack of adequate control for confounders. The findings from our study indicate that the burden of post-TB among residents aged over 15 years is substantial. In our study, the proportion of chronic respiratory symptoms in post-TB cases was nearly two times that of non-affected individuals: this can have a

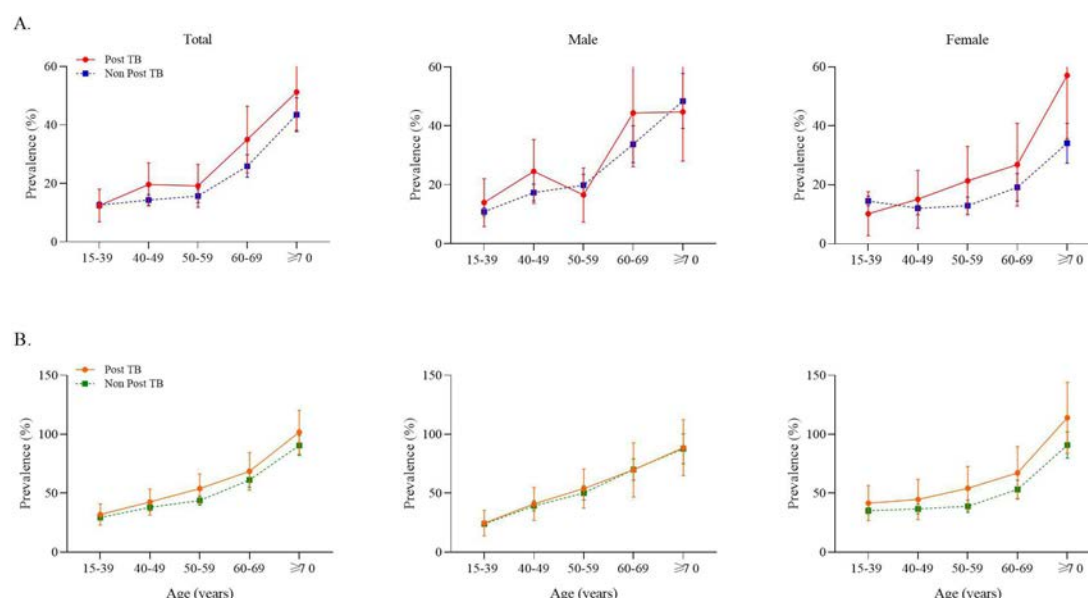


Figure 2 Standardised prevalence of airflow obstruction and small airway dysfunction in subjects based on history of post-TB. (A) Standardised prevalence of airflow obstruction. (B) Standardised prevalence of small airway dysfunction. Dots represent mean prevalence and error bars represent 95% CI. TB, tuberculosis.

negative impact on quality of life. Subjects with Post-TB also had more chronic comorbidities. Also, all lung parameters were significantly decreased in Post-TB subjects, even when a BD was used. We confirm that up to half of Post-TB people suffer from chronic and clinically relevant pulmonary function impairment and, in a majority of patients with airflow obstruction, obstruction was moderate to severe.^{24–27} In most cases, pulmonary function impairment remains undiagnosed and untreated, possibly resulting in an increased mortality compared with the standard population.^{28–29} Currently, there is much to do regarding the long-term medical and socioeconomic consequences of chronic lung function abnormalities after post-TB.³⁰

There were also few studies reported post-TB was associated with a higher risk of airflow obstruction. The study from 13 geographically diverse, low-resource settings recruiting participants reported the adjusted odds of 3.78 times higher among those with previous tuberculosis disease than those without a history of tuberculosis disease.⁶ Data from Korea National Health and Nutrition Examination Survey reported that airflow obstruction was associated with both a history and TB lesions on chest X-ray (OR 4.47, 95% CI 3.07 to 6.51) after adjustment for some confounders.⁷ The finding from Burden of Obstructive Lung Disease (BOLD) results showed that a self-reported history of tuberculosis was associated with airflow obstruction (adjusted OR 2.51, 95% CI 1.83 to 3.42).⁸ A cross-sectional analysis of the Guangzhou Biobank Cohort Study reported prior TB remained independently associated with an increased risk of airflow obstruction (OR: 1.37; 95% CI 1.13 to 1.67).⁹ The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study found participants with a medical history of tuberculosis were 2.3 times more likely to present airflow obstruction than those without such a diagnosis.¹⁰ However, these studies included participants aged over 35 years

old, incorporated no post-BD testing, used different definitions of post-TB. In the present study with a rigorous sampling design and strictly quality control, we found a nearly 1.31 time increase in risk of airflow obstruction in post-TB subjects after adjusting for confounders, and a stronger association in never smokers (OR: 1.37; 95% CI 1.04 to 1.78). Besides, airflow obstruction was present in 21.3% of post-TB cases, which are consistent with a recent meta-analysis reporting a pooled prevalence of COPD in patients with post pulmonary TB of 21% (95% CI: 16% to 25%)⁵ and another study from low- income and middle- income countries reporting COPD was more common (25.7%) among those with previous tuberculosis than those without a history of tuberculosis.⁶ Therefore, for vast majority of patients after TB, the development of adjuvant interventions to prevent or to suspend further deterioration of lung function in individuals with post-TB could be an essential tool.

Small airway dysfunction is characterised by premature airway closure and air trapping, regional heterogeneity and exaggerated volume dependence of airflow limitation. A study emphasised that small airway dysfunction preceded both the spirometric evidence of COPD and detection of emphysema by CT and considered as a precursor of COPD and asthma.³¹ The mechanisms are potential involvement of vasculature within the bronchovascular bundle in and around small airways after TB.³² Health professionals should possibly play a more active role in the detection of small airway dysfunction after pulmonary TB. We still found that post-TB subjects with a spirometric restrictive pattern had frequent sputum, recurrent wheezing, lower oxygen saturation and severe pulmonary lung function indices. It is proposed that a chronic inflammatory response and long-term anatomic alterations induced by pulmonary tuberculosis are the main pathological basis for airflow obstruction and restriction pattern.^{33–35} Chronic

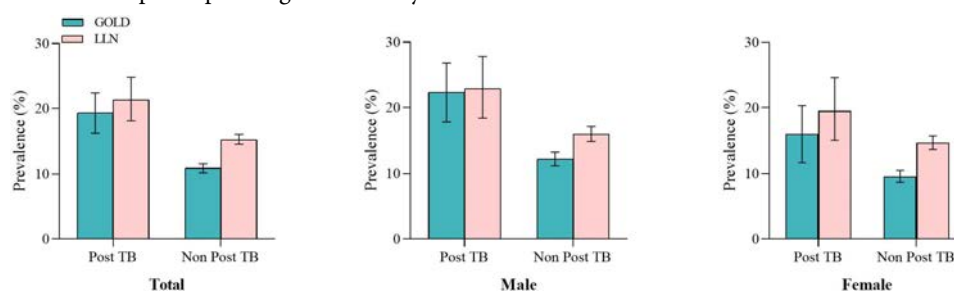


Figure 3 Prevalence of airflow obstruction based on two different diagnostic criteria for airway obstruction (GOLD and LLN) according to history of post-TB. Bars represent mean prevalence and error bars represent 95% CI. TB, tuberculosis.

Table 2 Characteristics of participants according to AO and post-TB status

Variables	P-TB (+)/AO (+) (n=130)	P-TB (-)/AO (+) (n=1230)	P-TB (+)/AO (-) (n=480)	P-TB (-)/AO (-) (n=6840)	P value*	P value†
Male	75 (57.7%)	627 (51.0%)	253 (52.7%)	3318 (48.5%)	0.519	0.075
Age group, years	53.90 (14.66)	42.34 (16.74)	48.07 (15.13)	38.98 (14.81)	<0.001	<0.001
City dwellers	53 (40.8%)	280 (22.8%)	203 (42.5%)	2300 (33.8%)	<0.001	<0.001
Education level						
Primary school and lower	93 (71.5%)	576 (46.8%)	269 (56.0%)	2936 (42.9%)	<0.001	<0.001
Middle and high school	30 (23.1%)	517 (42.0%)	150 (31.3%)	2708 (39.6%)		
College and higher	7 (5.4%)	137 (11.2%)	61 (12.7%)	1196 (17.5%)		
Smoking status						
Never smoker	85 (65.4%)	857 (69.7%)	320 (66.7%)	5009 (73.3%)	0.595	0.002
Ever smoker	45 (34.6%)	373 (30.3%)	160 (33.3%)	1828 (26.7%)		
History of asthma	16 (12.3%)	28 (2.3%)	16 (3.3%)	90 (1.3%)	0.428	0.005
Respiratory symptoms						
Frequent cough	30 (23.3%)	131 (10.7%)	79 (16.5%)	626 (9.3%)	0.001	<0.001
Sputum	31 (24.0%)	125 (10.2%)	79 (16.6%)	625 (9.2%)	<0.001	<0.001
Recurrent wheezing	18 (14.0%)	65 (5.3%)	36 (7.5%)	245 (3.6%)	0.079	<0.001
Dyspnoea in daily life	48 (37.2%)	257 (20.9%)	150 (31.4%)	1313 (19.4%)	<0.001	<0.001
At least one of the symptoms	64 (49.6%)	362 (29.5%)	220 (46.0%)	1897 (28.1%)	<0.001	<0.001
CAT score‡						
<10	22 (17.1%)	322 (26.3%)				
≥10	107 (82.9%)	904 (73.7%)				
Lung function parameters						
FVC post-BD, L	3.53 (1.11)	3.85 (1.02)	3.58 (0.99)	3.71 (0.94)	<0.001	0.004
FVC post-BD % pred	106.52 (28.16)	108.47 (24.20)	106.11 (24.83)	103.42 (21.89)	0.052	0.012
FEV ₁ post-BD, L	2.17 (0.85)	2.48 (0.79)	2.98 (0.85)	3.17 (0.82)	<0.001	<0.001
FEV ₁ post-BD % pred	79.41 (26.39)	83.14 (21.53)	106.28 (26.27)	104.77 (22.42)	<0.001	0.157
FEV ₁ /FVC post-BD, %	60.60 (10.44)	64.15 (9.99)	83.22 (7.08)	85.66 (6.86)	<0.001	<0.001
MMEF post-BD % pred	34.59 (17.63)	45.21 (73.41)	77.95 (32.87)	84.60 (52.50)	<0.001	0.013
FEF _{50%} post-BD % pred	40.74 (18.44)	47.01 (17.64)	94.84 (30.86)	95.53 (27.09)	<0.001	0.587
FEF _{75%} post-BD % pred	41.87 (34.86)	48.82 (25.95)	96.58 (57.56)	99.72 (45.9)	<0.001	0.147
SpO ₂ , %	92.24 (6.60)	94.58 (4.68)	91.17 (6.32)	93.25 (5.31)	<0.001	<0.001

Data are expressed as number (%) or mean (SD).

*P value difference between post-TB without airflow obstruction and airflow obstruction without post-TB.

†P value difference between normal population and post-TB without airflow obstruction.

‡CAT score difference for $p < 0.001$.

AO, airflow obstruction; CAT, chronic obstruction pulmonary disease assessment test; FEF, forced expiratory flow; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; post-BD, post-bronchodilator; P-TB, post-tuberculosis; P-TB(-)/AO(+), airflow obstruction without post-TB; P-TB(-)/AO(-), normal population without airflow obstruction and post-TB; P-TB(+)/AO(-), post-TB without airflow obstruction; P-TB(+)/AO(+), airflow obstruction with post-TB; SpO₂, oxyhemoglobin saturation.

residual or recurrent inflammation-induced narrowing of airways, peribronchial fibrosis, extensive fibrosis and stiffening of the lung parenchyma after tuberculosis contribute to the functional findings reported.^{36, 37} Indeed, there was an increased odds for small airway dysfunction in post-TB subjects studied.

Our study has important public health implications. Improving detection and treatment of TB should be implemented in China, particularly in areas with poor economic and health conditions. The objectives are not only effectively controlling of TB per se but also decreasing its long-term impacts on lung function, respiratory symptoms and quality of life through professional management, early pulmonary function and chest imaging. The importance of the interrelationship between post-TB and chronic airflow obstruction has been clearly illustrated in our study, especially among never smokers. Further studies are required to better determine the role of inhaled or even systemic steroids in patients with TB in whom airway obstruction is detected.

There are some limitations to our study. First, the cross-sectional design of this study cannot formally establish the temporal sequence and causal relationship between post-TB and airflow obstruction. Longitudinal studies are needed in order to determine

for how long and how often lung function impairment persists after TB. Second, ATS/ERS recommendations define the presence of a restrictive pulmonary disorder as having a total lung capacity (TLC) below the fifth percentile of predicted value. However, performing plethysmography or helium dilution measurements in a large study population such as ours is unrealistic. Using FVC as a surrogate for TLC is most often accepted in studies on restrictive pulmonary disorders. Third, the FEF_{50%} predicted value was automatically reported from our spirometer and derived from the European Community for Steel and Coal report in 1993.³⁸ The equation is more appropriate for adults aged 18–70 years, so there may be a bias for older or younger people. Fourth, bronchiectasis has been shown to be associated with a history of TB and may be associated with small airway dysfunction.³⁹ However, chest CT was rarely available because of our resource-limited setting. Furthermore, a history of bronchiectasis was self-reported by only 14 participants precluding any further analysis. Finally, it is important to note that our findings relate to post-TB defined by self-reported history and radiological changes on chest radiographs. The extent of TB lesions on chest radiographs could not be evaluated due to limited availability of CT scans, and the definition of radiologic

Table 3 Adjusted associations for airflow obstruction according to history of post-TB in participants aged ≥ 15 years

	Non-post-TB	Post-TB	P value
Overall subjects			
Airflow obstruction	1230	130	
Crude OR (95% CI)	1.00 (ref)	1.50 (1.22 to 1.83)	<0.001
Adjusted OR (95% CI)*	1.00 (ref)	1.31 (1.05 to 1.62)	0.013
Restrictive pattern	1374	99	
Crude OR (95% CI)	1.00 (ref)	0.94 (0.75 to 1.17)	0.613
Adjusted OR (95% CI)*	1.00 (ref)	1.02 (0.80 to 1.28)	0.865
Small airway dysfunction†	2993	297	
Crude OR (95% CI)	1.00 (ref)	1.59 (1.35 to 1.88)	<0.001
Adjusted OR (95% CI)*	1.00 (ref)	1.28 (1.07 to 1.53)	0.006
Never smokers			
Airflow obstruction	857	85	
Crude OR (95% CI)	1.00 (ref)	1.55 (1.20 to 1.98)	<0.001
Adjusted OR (95% CI)‡	1.00 (ref)	1.37 (1.04 to 1.78)	0.023
Restrictive pattern	1005	65	
Crude OR (95% CI)	1.00 (ref)	0.92 (0.69 to 1.20)	0.575
Adjusted OR (95% CI)‡	1.00 (ref)	0.98 (0.73 to 1.30)	0.904
Small airway dysfunction	2143	205	
Crude OR (95% CI)	1.00 (ref)	1.78 (1.45 to 2.18)	<0.001
Adjusted OR (95% CI)‡	1.00 (ref)	1.47 (1.18 to 1.83)	0.001

*Adjusted OR: adjustments for age, sex, region and education plus history of asthma, and exposure to HAP and occupation and smoking status.

†Adjusted OR: adjusted OR except for smoking status.

‡Assessed in small airway dysfunction with data missing for 86 participants. HAP, household air pollution; TB, tuberculosis.

evidence may lack sensitivity and underestimate post-TB status. However, in a TB-prevalent region, presence of fibrotic scars or calcified nodules in the upper lobes is usually secondary to healed TB and is, thus, considered as specific.

In conclusion, post-TB status was associated with pulmonary function impairment, including airflow obstruction and small airway dysfunction, as well as with chronic respiratory symptoms. We also found that association between post-TB and pulmonary impairment was stronger among never smokers. Strategies must be developed in terms of research, prevention, earlier detection of functional impairment and management of post-TB patients as a way of preventing chronic pulmonary sequelae and disability.

Author affiliations

¹Department of Respiratory and Critical Care Medicine, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Hospital, Beijing, China

²Department of Respiratory and Critical Care Medicine, Peking University Fifth School of Clinical Medicine, Beijing, China

³Division of Pulmonary Diseases, Geneva University Hospital, Geneva, Switzerland

⁴Department of Intensive Care Medicine, Rehabilitation Research Center, Beijing Boai Hospital, Beijing, China

⁵Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China

⁶National Center for Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, Beijing, China

⁷Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

⁸Department of Respiratory Medicine, Capital Medical University, Beijing, China

Acknowledgements We acknowledge the following investigators for their continuous support, assistance and cooperation: Wang Miao from Beijing Anzhen Hospital, Hongsheng Zhang, Xiaomeng Li, Xiaoming Tan, and Aonan Li from Beijing Hospital, Zengwu Wang, Linfeng Zhang, and Xin Wang from Fu Wai Hospital, Yundai Chen, and Bin Feng from Chinese PLA General Hospital, Sinan Wu and Wenquan Liu from China-Japan Friendship Hospital.

Contributors YG, CW and TS conceived and designed the study. YG and CW supervised the study. ZX did the statistical analysis. All authors contributed to acquisition, analysis or interpretation of data. YG and ZX drafted the manuscript. All authors revised the report and approved the final version before submission. As a guarantor, YG accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was supported by the Ministry of Science and Technology of China (2018YFC1315101); Beijing Hospital Clinical Research 121 Project (BJ-2018-199).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institutional Review Board and Ethics Committee of Beijing Hospital (2013BJYYEC-042C-01). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- World Health Organization. Global tuberculosis report 2021, 2021.
- Chakaya J, Khan M, Ntouni F, et al. Global Tuberculosis Report 2020 - Reflections on the Global TB burden, treatment and prevention efforts. *Int J Infect Dis* 2021;113 Suppl 1:S7-12.
- De Matteis S, Jarvis D, Darnton A, et al. The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank cohort. *Eur Respir J* 2019;54:1900186.
- Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *The Lancet* 2009;374:733-43.
- Fan H, Wu F, Liu J, et al. Pulmonary tuberculosis as a risk factor for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ann Transl Med* 2021;9:390-90.
- Kamenar K, Hossen S, Gupta AN, et al. Previous tuberculosis disease as a risk factor for chronic obstructive pulmonary disease: a cross-sectional analysis of multicountry, population-based studies. *Thorax* 2022;77:1088-97.
- Choi CJ, Choi WS, Lee SY, et al. The definition of past tuberculosis affects the magnitude of association between pulmonary tuberculosis and respiratory dysfunction: Korea National health and nutrition examination survey, 2008-2012. *J Korean Med Sci* 2017;32:789-95.
- Amaral AFS, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J* 2015;46:1104-12.
- Lam K-bong H, Jiang CQ, Jordan RE, et al. Prior TB, smoking, and airflow obstruction: a cross-sectional analysis of the Guangzhou Biobank cohort study. *Chest* 2010;137:593-600.
- Menezes AMB, Hallal PC, Perez-Padilla R, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J* 2007;30:1180-5.
- Allwood BW, Stolbrink M, Baines N, et al. Persistent chronic respiratory symptoms despite TB cure is poorly correlated with lung function. *Int J Tuberc Lung Dis* 2021;25:262-70.
- Osman M, Welte A, Dunbar R, et al. Morbidity and mortality up to 5 years post tuberculosis treatment in South Africa: a pilot study. *Int J Infect Dis* 2019;85:57-63.
- Meghji J, Lesosky M, Joekes E, et al. Patient outcomes associated with post-tuberculosis lung damage in Malawi: a prospective cohort study. *Thorax* 2020;75:269-78.
- Guo Y, Xing Z, Shan G, et al. Prevalence and risk factors for COPD at high altitude: a large cross-sectional survey of subjects living between 2,100-4,700 M above sea level. *Front Med* 2020;7:1-10.
- Miller MR et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- Enright P, FEV1 and FVC repeatability goals when performing spirometry. *Prim Care Respir J* 2010;19:194-94.
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-Ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324-43.
- Singh D, Agustí A, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the gold science Committee report 2019. *Eur Respir J* 2019;53:1900164.
- Xiao D, Chen Z, Wu S, et al. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. *Lancet Respir Med* 2020;8:1081-93.
- Thumerelle C, Pouessel G, Errera S. Radiologic manifestations of pulmonary tuberculosis. *Archives de Pédiatrie* 2005;12:S132-6.
- State. TU/SoADo. Instruction to panel for completing chest X-ray and classification worksheet (DS-3024). Available: <http://www.wcdgov.ncidod/dq/dsforms/3024.htm> [Accessed 26 Nov 2009].
- Jung J-W, Choi J-C, Shin J-W, et al. Pulmonary impairment in tuberculosis survivors: the Korean National health and nutrition examination survey 2008-2012. *PLoS One* 2015;10:e0141230-12.
- Caballero A, Torres-Duque CA, Jaramillo C, et al. Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest* 2008;133:343-9.
- Allwood BW, van der Zalm MM, Amaral AFS, et al. Post-tuberculosis lung health: perspectives from the first International Symposium. *Int J Tuberc Lung Dis* 2020;24:820-8.
- Ravimohan S, Kornfeld H, Weissman D, et al. Tuberculosis and lung damage: from epidemiology to pathophysiology. *Eur Respir Rev* 2018;27:170077.
- Chushkin MI, Ots ON. Impaired pulmonary function after treatment for tuberculosis: the end of the disease? *J Bras Pneumol* 2017;43:38-43.
- Harries AD, Ade S, Burney P, et al. Successfully treated but not fit for purpose: Paying attention to chronic lung impairment after TB treatment. *Int J Tuberc Lung Dis* 2016;20:1010-4.
- Ranzani OT, Rodrigues LC, Bombarda S, et al. Long-Term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010-15: a population-based, longitudinal study. *Lancet Infect Dis* 2020;20:123-32.
- Miller TL, McNabb SJN, Hilsenrath P, et al. Personal and societal health quality lost to tuberculosis. *PLoS One* 2009;4:e5080-7.
- Hanania NA, Celi BR, Donohue JF, et al. Bronchodilator reversibility in COPD. *Chest* 2011;140:1055-63.
- Konstantinos Katsoulis K, Kostikas K, Kontakiotis T. Techniques for assessing small airways function: possible applications in asthma and COPD. *Respir Med* 2016;119:e2-9.
- Allwood BW, Rigby J, Griffith-Richards S, et al. Histologically confirmed tuberculosis-associated obstructive pulmonary disease. *Int J Tuberc Lung Dis* 2019;23:552-4.
- Oh JY, Lee YS, Min KH, et al. Difference in systemic inflammation and predictors of acute exacerbation between smoking-associated COPD and tuberculosis-associated COPD. *Int J Chron Obstruct Pulmon Dis* 2018;13:3381-7.
- Guidem E, Ikomey GM, Nkenfou C, et al. Chronic obstructive pulmonary disease (COPD): neutrophils, macrophages and lymphocytes in patients with anterior tuberculosis compared to tobacco related COPD. *BMC Res Notes* 2018;11:1-5.
- Allwood BW, Maasdorp E, Kim GJ, et al. Transition from restrictive to obstructive lung function impairment during treatment and follow-up of active tuberculosis. *Int J Chron Obstruct Pulmon Dis* 2020;15:1039-47.
- Jin J, Li S, Yu W, et al. Emphysema and bronchiectasis in COPD patients with previous pulmonary tuberculosis: computed tomography features and clinical implications. *Int J Chron Obstruct Pulmon Dis* 2018;13:375-84.
- Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration* 2013;86:76-85.
- Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report Working Party standardization of lung function tests, European community for steel and coal. official statement of the European respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
- Byrne AL, Marais BJ, Mitnick CD, et al. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015;32:138-46.

ARTIGO ORIGINAL

Além fronteiras: sobrevivência à fibrose quística entre Austrália, Canadá, França e Nova Zelândia

Adèle Coriati,¹ Xiayi Ma,¹ Jenna Sykes,¹ Sanja Stanojevic,² Rasa Ruseckaite,³ Lydie Lemonnier,⁴ Clémence Dehillotte,⁴ Jan Tate,⁵ Catherine Ann Byrnes,^{6,7} Scott C Bel,^{8,9} Pierre Regis Burgel,^{10,11,12} Anne L Stephenson^{1,13,14}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/thorax-2022-219086>).

For numbered affiliations see end of article.

Correspondence to

Dr Anne L Stephenson, Dept. of Respiratory, St Michael's Hospital, Toronto, Canada; Anne.Stephenson@unityhealth.to

Received 20 April 2022

Accepted 23 August 2022

Published Online First

15 September 2022



► <http://dx.doi.org/10.1136/thorax-2022-219086>



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY. Published by BMJ.

To cite: Coriati A, Ma X, Sykes J, et al. *Thorax* doi:10.1136/thoraxjnl-2022-219086

RESUMO

Contexto A esperança média de vida das pessoas com fibrose quística (FQ) varia consideravelmente tanto dentro como entre países. O objetivo deste estudo foi comparar a sobrevivência entre países com sistemas de cuidados de saúde de pagador único, tendo simultaneamente em conta os marcadores de gravidade da doença.

Métodos Este estudo de coorte utilizou dados de registos nacionais de FQ reputados na Austrália, Canadá, França e Nova Zelândia, entre 2015 e 2019. A idade média de sobrevivência para cada um destes quatro países foi estimada com recurso ao método Kaplan-Meier. Para comparar o risco de morte entre o Canadá, França e Austrália depois de ajustado aos fatores de prognóstico foi utilizado o modelo de riscos proporcionais de Cox. Devido ao baixo número de mortes, a Nova Zelândia não foi incluída nos modelos ajustados finais.

Resultados Entre 2015 e 2019, foram incluídas ao todo 14 842 pessoas (3537 da Austrália, 4434 do Canadá, 6411 de França e 460 da Nova Zelândia). A idade média de sobrevivência era mais elevada em França 65,9 anos (IC 95%, 59,8 a 76,0) vs 53,3 anos (IC 95%, 48,9 a 59,8) na Austrália, 55,4 anos (IC 95%, 51,3 a 59,2) no Canadá, 54,8 anos (IC 95%, 40,7 a não disponível) na Nova Zelândia. Depois de ajustado a fatores de nível individual, o risco de morte foi significativamente mais elevado no Canadá (HR 1,85, 95% CI: 1,48 a 2,32; $p < 0,001$) e Austrália (HR 2,08, IC 95%, 1,64 a 2,64; $p < 0,001$) vs França.

Interpretação Observámos uma sobrevivência significativamente mais elevada em França quando comparada com países com sistemas de saúde de pagador único. A idade média de sobrevivência em França excedia os 60 anos de idade apesar de ter a maior proporção de pacientes demasiado magros, o que se poderá dever a diferenças na disponibilidade de um transplante.

INTRODUCTION

Between country comparisons of morbidity and mortality can be useful to inform policies at a national level. Prior research has shown large differences in prognosis for those living with cystic fibrosis (CF) when comparing high-income countries with low/middle-income countries as well as comparisons between high-income nations.^{1–3} Although many countries with established CF registries produce annual registry reports, direct comparisons are often inappropriate or not possible due to variation in definitions or differing categorisation of key metrics used to monitor health. Even with outcomes that have an unequivocal definition, such as mortality, direct comparisons can be challenging due to variations in data processing, missing death data or a lack of clarity around those included or excluded from the survival analyses.⁴ Furthermore, when comparing survival metrics, many national registry reports

Key messages

What is already known on this topic

► International comparisons have the potential to yield important results, as distinct differences, as well as similarities, in cystic fibrosis care delivery exist in different countries.

What this study adds

► After accounting for the variation in patient characteristics, cystic fibrosis survival was the highest in France compared with Canada, Australia and New Zealand.

How this study might affect research, practice or policy

► Disparities in outcomes between countries could be explained by modifiable factors such as access to transplant.

lack median age of survival estimates making survival comparisons impossible.⁵

International comparisons of CF populations can ultimately change practice—a survival comparison between Toronto and Boston discovered a higher age of survival in Toronto and led to the recommendation of the high fat diet in the 1980s⁶. More recently, Stephenson *et al* confirmed a 10-year survival advantage for Canadians living with CF compared with similar people in the USA after accounting for prognostic factors.³ The same group found that transplantation and post-transplant survival explained 30% of the survival gap between the countries highlighting a potentially modifiable factor that could boost survival for individuals living with CF in the USA.⁷ Transplantation, however, does not fully explain the Canada–USA survival gap and another distinct difference between the countries relates to the model of healthcare delivery as Canadians have access to a universal, single-payer healthcare system whereas Americans use a multipayer healthcare scheme which could limit access to medical care depending on insurance coverage and financial ability. The Canada–USA survival study found that individuals in the USA with no insurance or on medicare/medicaid were more likely to die than people in the USA with private insurance. Furthermore, there was no statistically significant difference in risk of death between those with private insurance in the USA and Canadians.³ Comparing health metrics between countries with similar healthcare models could minimise this as a contributing factor.

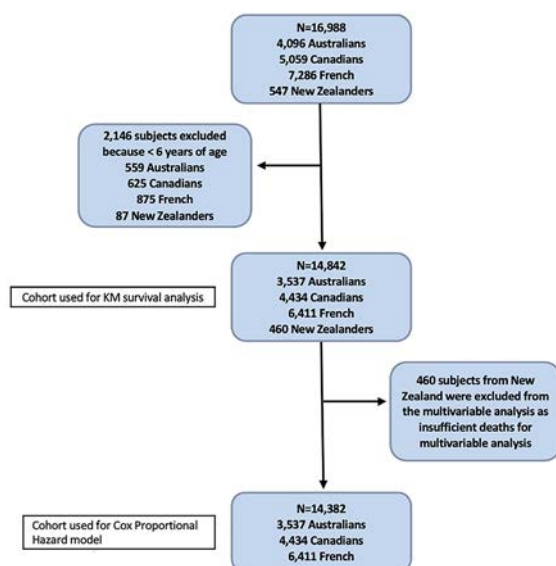


Figure 1 Cohort creation 2015–2019. KM, Kaplan-Meier.

The main objective of our study was to directly compare demographic and clinical characteristics as well as survival outcomes in a contemporary cohort of individuals living with CF in countries with single-payer healthcare systems namely, Australia, Canada, France and New Zealand (NZ). We hypothesise that there will be no statistically significant difference in survival between the countries.

METHODS

Design

This population-based cohort study used four established, national longitudinal CF registries: Australian CF registry (ACFDR), Canadian CF registry (CCFR), French CF registry (FCFR) and NZ CF registry (NZCFR). Individuals captured in each of the registries provide informed consent to have their data collected and used for research purposes.

Study period

A contemporary period between 1 January 2015 and 31 December 2019 was used.

Data resources

The ACFDR is managed by Monash University and has been in existence since 1998. The registry captures data on more than 4500 individuals followed in 23 CF centres which is reported to be at least 90% of the CF population. The CCFR, managed by CF Canada, has been in existence since the early 1970s and is estimated to capture 98% of the CF population with a low rate of lost-to-follow-up (~5%). The registry currently contains annual records on more than 6700 unique individuals with CF who are followed in the 42 Canadian CF clinics. The FCFR is managed by the Vaincre la Mucoviscidose. Since its inception in 1992, the registry has data on more than 9450 individuals followed in 47 CF centres, capturing at least 95% of the French CF population. The NZCFR is managed by CF NZ and follows more than 540 individuals. Established in 2011, the NZCFR registry captures data from 19 NZ clinics. It is reported that about 98% of New Zealanders with CF are followed in the NZCFR. Registry data undergo routine validation checks to ensure that they are free of duplicates and errors.⁵ Only individuals with a diagnosis of CF were included in this analysis while individuals with cystic fibrosis transmembrane conductance regulator (CFTR)-related disease or cystic fibrosis screen positive, inconclusive diagnosis were excluded.

Demographic and clinical data are recorded annually. Demographic data included date of birth, sex, age at diagnosis, newborn screening status (NBS), CFTR variant, pancreatic status and date

of death. Clinical measurements include lung function, nutritional status, sputum bacteriology, number of hospitalisations or home intravenous antibiotic therapy, date of transplant as well as organ transplanted.

Variable definitions

Variable definitions and method of data collection in the four registries were evaluated by the research team to create a harmonised dataset for analysis. Date of CF diagnosis was imputed using date of birth plus 30 days when missing and categorised as age at diagnosis as <2 and ≥2 years of age.⁸ CF genotype was classified as Phe508del homozygous, Phe508del heterozygous, other or missing. Lung function, specifically the forced expiratory volume in 1 s (FEV₁), was recorded in litres and interpreted as percent predicted (ppFEV₁) calculated using Global Lung Function Initiative reference equations.⁹ The best annual ppFEV₁ was selected for each individual each year. Body mass index (BMI) was calculated for adults over 19 years of age as weight (kg)/height² (m). BMI percentiles were calculated for individuals ages 2–19 years of age by using the Centre for Disease Control growth charts.¹⁰ Annual BMI or BMI centiles were calculated using data on the closest date within 3 months of the best lung function measurement. Individuals were categorised as underweight (BMI <19 kg/m² or BMI %ile ≤12%), adequate weight (BMI between ≥19 kg/m² and ≤24.9 kg/m² or BMI %ile between >12% and <85%) or overweight (BMI >24.9 kg/m² or BMI %ile ≥85%).^{10,11} Severe pulmonary exacerbations were defined as the administration of intravenous antibiotics in the hospital and/or at home and were recorded as the number of events per year. Pancreatic insufficiency (PI) was determined by pancreatic enzyme use recorded in the registries. The presence of *Burkholderia cepacia* (*B. cepacia*) complex or *Pseudomonas aeruginosa* (*P. aeruginosa*) was considered positive if these bacteria were recorded at least once each year.¹²

Statistical analysis

Median and IQR were used to summarise continuous variables whereas frequency and proportion were used to summarise categorical variables. A period approach was used to estimate median age of survival over a 5-year window from 2015 to 2019. The Kaplan-Meier (KM) method was used to calculate the probability of survival in each of the four countries. KM survival curves were generated for the following subgroups: PI, pancreatic sufficiency and those who were homozygous deltaF508. Observations were left truncated on 1 January 2015 or the date of diagnosis if the diagnosis occurred within the time window. The follow-up period ended on 31 December of the last observation recorded or death date.

Differences in survival between the countries were further explored by adjusting for demographic and clinical characteristics using a multivariable Cox proportional hazards (PH) model. In New Zealand, only 21 deaths were recorded, and thus it was not possible to include this country in the multivariable analysis. The multivariable model, which included both transplanted and non-transplanted individuals, was adjusted for time-independent characteristics specifically sex, age at diagnosis, NBS, pancreatic status, transplant status, baseline ppFEV₁ and baseline BMI. 'Baseline' was defined as the last available measurement for those who were not transplanted, or before death or the end of the follow-up period. For those who were transplanted, baseline is defined as before transplant if transplant occurred in 2013 or later, otherwise baseline pre-transplant data were imputed using multiple imputation for transplanted recipients. Individuals <6 years of age were excluded as this age group does not reliably perform lung function testing. Missing data were imputed using multiple imputation with chained equations using the R package mice (V.3.7.0). All variables except for post-transplant specific variables were included in the imputation model for predicting the missing values. Ten imputed datasets were created and the results were pooled as outlined in Rubin.¹³ The PHs assumption was checked by testing the independence between the Schoenfeld

Table 1 Characteristics of individuals in Canada, France, Australia and New Zealand at the most recent measurement within the study window (2015–2019; n=14 842)*

	Australia	Canada	France	New Zealand
Total number of individuals	3537	4434	6411	460
Sex				
Women	1676 (47.4)	2025 (45.7)	3048 (47.5)	209 (45.4)
Men	1861 (52.6)	2409 (54.3)	3363 (52.5)	251 (54.6)
Age at diagnosis				
<2 years old	3010 (85.1)	2809 (63.4)	4477 (69.8)	349 (75.9)
≥2 years old	527 (14.9)	1625 (36.6)	1934 (30.2)	111 (24.1)
%Imputed	533 (15.1%)	79 (1.8%)	205 (3.2%)	14 (3.0%)
Newborn screening	1805 (51.0)	611 (13.8)	2786 (43.5)	218 (47.4)
Genotype				
Phe508del homozygote	1632 (46.1)	2089 (47.1)	2615 (40.8)	228 (49.6)
Phe508del heterozygote	1418 (40.1)	1775 (40.0)	2755 (43)	166 (36.1)
Other	258 (7.3)	503 (11.3)	958 (14.9)	48 (10.4)
Missing	229 (6.5)	67 (1.5)	83 (1.3)	18 (3.9)
Mutation class				
Class I–III	2980 (84.3%)	3754 (84.7%)	5390 (84.1%)	392 (85.2%)
Class IV–V	291 (8.2%)	534 (12%)	741 (10%)	35 (7.6%)
Unclassifiable/missing	266 (7.5%)	146 (3.3%)	321 (5%)	33 (7.2%)
Pancreatic status (ever/never)				
Insufficient	2770 (78.3)	3690 (83.2)	5749 (89.7%)	368 (80.0)
Sufficient	602 (17.0)	744 (16.8)	662 (10.3%)	87 (18.9)
Missing	165 (4.7)	0	0	5 (1.1)
Microbiology (ever/never)				
<i>P. aeruginosa</i>	N/A	1793 (40.4)	2652 (41.4)	166 (36.1)
<i>B. cepacia</i> complex	N/A	352 (7.9)	271 (4.2)	45 (9.8)
Intravenous antibiotic courses/year†				
0	1760 (53.3%)	2659 (65.4%)	3246 (56.6%)	237 (52.4%)
1–2	967 (29.3%)	952 (23.4%)	1204 (21%)	123 (27.2%)
≥ 3	572 (17.3%)	450 (11.1%)	1287 (22.4%)	92 (20.4%)
ppFEV ₁ ‡ median, IQR	82.9 (57.7–96.5)	75.9 (51.7–93.2)	77.5 (53.5–94.2)	83.4 (59.7–98)
<40	325 (9.9%)	546 (13.4%)	782 (13.6%)	49 (10.8%)
40–69	698 (21.2%)	1021 (25.1%)	1413 (24.6%)	94 (20.8%)
≥70	1965 (59.6%)	2054 (50.6%)	3215 (56%)	275 (60.8%)
Missing	311 (9.4%)	440 (10.8%)	327 (5.7%)	34 (7.5%)
BMI categories§				
Underweight	274 (8.3%)	387 (9.5%)	1062 (18.5%)	39 (8.6%)
Normal	2074 (62.9%)	2502 (61.6%)	3875 (67.5%)	303 (67%)
Overweight	656 (19.9%)	814 (20%)	577 (10.1%)	81 (17.9%)
Missing	295 (8.9%)	358 (8.8%)	223 (3.9%)	29 (6.4%)

*Data are presented as n (%), unless indicated otherwise. Clinical variables are summarised based on the latest pre-transplant observation within the study period. There were 1293 patients who had no pre-transplant FEV₁, % predicted, BMI or courses of intravenous antibiotic clinical measurements recorded because they were transplanted before 2015 and individuals were excluded from the table summary (238 (6.7%) in AUS, 373 (8.4%) in CAN, 674 (10.5%) in FRA and 8 (1.7%) in NZ.

†Intravenous courses includes antibiotic therapy given in hospital and at home.

‡Percent predicted forced expiratory volume in 1 s (ppFEV₁) was calculated using the Global Lung Function Initiative reference equation. The best ppFEV₁ was chosen for each the year.

§Body mass index (BMI for adults) or BMI percentile (for children) closest to the chosen FEV₁ was selected. Individuals were categorised as underweight (BMI <19 kg/m² or BMI %ile ≤12%), adequate weight (BMI between ≥19 kg/m² and ≤24.9 kg/m² or BMI %ile between >12% and <85%) or overweight (BMI >24.9 kg/m² or BMI %ile ≥85%).

B. cepacia complex, Burkholderia cepacia complex; AUS, Australia; BMI, body mass index; CAN, Canada; FEV₁, forced expiratory volume in 1 s; FRA, France; N/A, not available; NZ, New Zealand; *P. aeruginosa*, *Pseudomonas aeruginosa*.

residuals and time variable and the assumption of linearity was checked by plotting the Martingale residuals. All statistical analysis was done using the R software (V.3.6.2).¹⁴ All p values are two-sided and assessed for significance at p<0.05 unless otherwise stated.

RESULTS

Comparison of study populations between countries

The cohort flow diagram for individuals included in the analysis can be seen in figure 1. Demographic and clinical and characteristics of each CF population are reported in table 1. Between 2015 and 2019,

Table 2 Survival, deaths and transplants in Canada, France, Australia and New Zealand (2015–2019; n=14842)*

	Australia	Canada	France	New Zealand
Total number of individuals, n	3537	4434	6411	460
Median age of survival, years (95% CI)	53.3 (49.7 to 59.8)	55.4 (51.3 to 59.2)	65.9 (59.8 to 76.0)	54.8 (40.7 to NA)
Transplants†, n (%)	413 (11.7)	589 (13.3)	1061 (16.5)	31 (6.7)
Paediatric, n (% of total transplants)	20 (4.8)	27 (4.6)	99 (9.3)	1 (3.2)
Adult, n (% of total transplants)	393 (95.2)	562 (95.4)	962 (90.7)	30 (96.8)
Age at transplant, years	30.6 (24.8–38.3)	29.7 (24.2–37.1)	26.9 (22.2–33.6)	30 (25.7–34.1)
Paediatric (≤18 years)	15.2 (14.1–16.6)	16 (14.5–16.9)	16.1 (13.7–16.9)	17 (17–17)
Adult (>18 years)	31 (25.7–38.8)	30.1 (24.9–37.6)	28.1 (23.7–34.1)	30.1 (25.8–34.2)
Deaths, n (%)	178 (5)	257 (5.8)	241 (3.8)	21 (4.6)
Death without transplant, n (% of total deaths)	97 (54.5)	149 (58)	98 (40.7)	16 (76.2)
Death after transplant, n (% of total deaths)	81 (45.5)	108 (42)	143 (59.3)	5 (23.8)
Age at death, years	33.7 (25.4–44.1)	34.7 (25.8–45.9)	31.9 (24.3–41.9)	34.7 (24.8–44.2)
Age at death without transplant, years	32.4 (23.8–44)	31.7 (22.7–45.4)	30.3 (23.8–42.3)	34.6 (26.6–45.4)
Age at death after transplant, years	35.3 (26.8–44.1)	38.8 (31.1–47.2)	33 (25.1–41.5)	35.7 (21.9–37.5)

*Data are presented as median (IQR), unless indicated otherwise.

†This represents individuals who were followed in the registry between 2015 and 2019 and had received a transplant at any time point. NA, not available.

there were a total of 14842 subjects included in the analysis: 3537 individuals with CF included from Australia, 4434 in Canada, 6411 in France and 460 in New Zealand. The percentage of individuals who were diagnosed through newborn screening was the lowest in Canada (13.8%) compared with the other countries. France had the lowest proportion of individuals who were homozygous for Phe508del (42%) and the highest percentage of people with 'other' mutations (13.9%). The proportion of individuals who were underweight was the highest in France (18.5%) compared with the other countries whereas the median ppFEV₁ was lowest in Canada.

Transplanted patients were included in the study window but the transplant itself may have occurred prior to or during the study period of 2015–2019. Of the individuals followed in the study period, 413 (11.7%) had received a lung transplant in Australia compared with 589 (13.3%) in Canada, 1061 (16.5%) in France and 31 (6.7%) in New Zealand (table 2). Age at transplant and age at death were the lowest in France. The proportion of deaths without transplant was higher than the proportion of death post-transplant for all countries except for France where the opposite was observed (table 2).

Survival comparisons

The KM survival curves for each country and by subgroups are shown in figure 2 and online supplemental figure S1. The median

age of survival was highest in France (65.9 years; 95% CI: 59.8 to 76.0 years) compared with Australia (53.3 years; 95% CI: 49.7 to 59.8), Canada (55.4 years; 95% CI: 51.3 to 59.2) and New Zealand (54.8 years; 95% CI: 40.7 to NA) (figure 2, table 2).

The Cox proportional modelling analysis excluded New Zealand therefore, included a total of 14382 subjects with 178 deaths in Australia, 257 deaths in Canada and 241 deaths in France. The univariable analysis showed the risk of death was higher in Canada (HR 1.35, 95% CI: 1.13 to 1.62; p<0.001) and Australia (HR 1.45, 95% CI: 1.2 to 1.76; p<0.001) compared with France. After adjusting for sex, age at diagnosis, NBS, pancreatic status and lung transplant status, baseline ppFEV₁ and BMI category, the risk of death was significantly higher in Canada (HR 1.79, 95% CI: 1.44 to 2.22; p<0.001) and Australia (HR 2.04, 95% CI: 1.61 to 2.59; p<0.001) compared with France. There was no evidence of a difference in survival between Canada and Australia (HR 0.88, 95% CI: 0.68 to 1.13; p=0.27). (online supplemental figure S2)

DISCUSSION

Using contemporary CF data, our study identified a survival gap between people living in high-income countries with similar healthcare systems. France had the highest recorded median age of survival of the four countries, surpassing 60 years in the contemporary time window between 2015 and 2019. Although there were some notable differences in individual characteristics between the countries, after adjusting for these factors, the risk of death remained higher in Canada and Australia compared with France despite the countries having national healthcare systems. The exceptional survival in France is despite having the highest proportion of underweight individuals which has consistently been found in the literature to be strong predictor of worse outcomes in CF. Furthermore, these data were collected prior to the availability of ellexacaftor–tezacaftor–ivacaftor which has been shown to improve lung function and is predicted to increase future survival estimates.¹⁵

Through international comparisons, differences in health outcomes raise questions about the reasons for such disparities. It is unlikely that a single factor can explain why one country has better survival than another country. Although universal, government-funded healthcare allows broad access to medical care, this does not necessarily translate into full access to chronic medications known to improve health and there are distinct differences in this regard between the countries studied. France has an extensive, government-funded medication programme that minimises barriers to accessing CF medications. In Canada, drug coverage

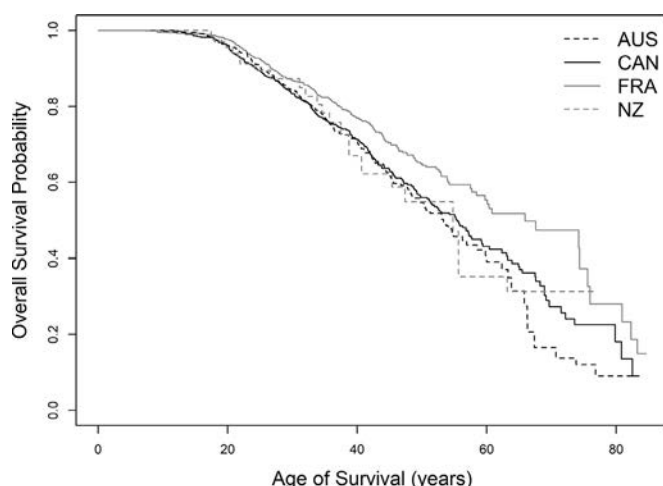


Figure 2 Overall survival probability in cystic fibrosis between Canada, France, Australia and New Zealand (2015–2019; n=14842). AUS, Australia; CAN, Canada; FRA, France; NZ, New Zealand.

plans vary between provinces with some provinces having more extensive coverage of CF medications while others are more restrictive. Canadians with private drug insurance through employment may have coverage for a broad list of medications at no additional cost to them. While others without drug insurance would have to pay out-of-pocket to access certain CF medications thus limiting access. Access to medication in Australia and New Zealand is, in essence, a hybrid between Canada and France with the majority of medications being covered by healthcare funders with a nominal cost to patients. Such differential access to medications could explain differences in health outcomes as therapies have been linked to improved lung function and reduced exacerbations, both of which are closely associated with survival.^{16 17} Unfortunately, we did not have complete medication data for the study period across all registries that would allow a robust comparison to answer this question, but this would be an important line of investigation for future research.

Given that the majority of deaths in CF are due to progressive lung disease, lung transplantation can dramatically and quickly alter the trajectory of the disease. Transplantation explained 30% of the survival gap between Canada and the USA, again highlighting the importance of this potentially modifiable therapeutic option as a means to increase survival for individuals with CF.⁷ Our data showed that France had the highest proportion of transplant recipients in the study window. Furthermore, France was the only country that had a lower proportion of deaths without transplant of all the countries compared with deaths that occurred after the opportunity for transplant. These data suggest that a significant proportion of individuals in need of transplant in France were able to receive this life-saving therapy. Interestingly, in 2007 France implemented a high emergency lung transplant (HELT) programme at a national level by the French Agence de la Biomedicine. When a patient corresponds to the criteria of HELT, their file is submitted to the Agency and examined by a panel of experts. If the experts confirm the eligibility to HELT, the patient is given national priority for 7 days; it can be extended by 7 days (total time 14 days) if no organ transplant was made available during the initial 7 days.¹⁸ Since this was implemented, the number of individuals dying on the transplant list in France dramatically decreased resulting in more transplants for those who needed them. This, in turn, decreased the number of individuals who died without transplant while the number of transplant recipients increased.¹⁹ Further, although patients transplanted from the HELT programme were critically ill, there was no negative impact on overall post-transplant survival compared with the survival prior to the implementation of the program.¹⁹ The HELT programme is unique to France and although medical need influences prioritisation on the transplant list in Canada, Australia and New Zealand, the process is less formalised when compared with the system adopted in France.

Unlike transplantation, the impact of NBS on survival estimates would not be evident for several decades until babies screened at birth reached an age where they would be at risk for death. NBS was introduced at different times depending on the country: France (~1989 for two regions, nationally in 2002), Australia (1981 in New South Wales, nationally in 2001) and New Zealand (~1983) versus Canada (~2007 in most provinces, nationally in 2018)^{20–23} and this is reflected in the proportion of individuals diagnosed through NBS by country. Furthermore, differential algorithms for NBS exist so it is possible that milder mutations may be identified in some countries compared with others which may impact survival estimates. However, when mutations were classified by functional class, the proportions were similar between the countries. Given paediatric mortality is not very prevalent, and most deaths occurred in adults, it is unlikely that NBS already had an effect of survival. This effect, if it exists, will need more time to be observed.

There is some evidence, although not consistently shown, that higher healthcare spending as determined by the percentage of gross domestic product (GDP), is associated with better health

outcomes.^{24 25} According to 2019 statistics, France spent 11.1% of GDP on healthcare compared with 10.8% for Canada, 9.8% for Australia and 9.1% for New Zealand. Such differences are small and are unlikely to explain such a large gap in survival as seen in our study. Furthermore, spending more on healthcare does not guarantee better outcomes. The USA spent the highest percentage of GDP on healthcare (~17%) in 2019, almost twice that of Canada, yet prior literature showed that Canadians with CF live on average 10 years longer than their US counterparts again suggesting that the reasons for international differences in survival are complex and multifactorial.

Our study has several strengths and limitations to consider. The detailed clinical information available in national registries allowed a methodologically rigorous approach to addressing international differences regarding survival and health outcomes in CF. A harmonised approach to variable definitions within the registries ensured appropriate and robust comparisons to allow adjustment for important confounding variables. The registries capture a national picture of individuals with CF with few individuals lost to follow-up. It is possible that individuals with CFTR-related disease were included within the registries but not clearly identified; however, this would represent a small number and would not be unique to any single country therefore minimising any potential bias. Certain data elements were either unavailable in all registries (ie, not captured at all) or were incompletely recorded specifically medication, microbiology and socioeconomic status thus we were unable to account for these factors in our analyses. Future analyses may take into consideration such factors since data collection in registries has expanded with enhanced granularity in recent years. As with all registries, there is a degree of missing data; however, where possible, original source documents were obtained to fill in the gaps and multiple imputation was used to inclusion of all available subjects in the multivariable model. Furthermore, our results were unchanged when we conducted a complete case analysis compared with those where we used multiple imputation. Finally, the variable availability of earlier CFTR modulator therapies (ie, lumacaftor–ivacaftor, tezacaftor–ivacaftor) coupled with inconsistent data capture of these elements across all four registries made it impossible to accurately summarise the data across the study period. Although ivacaftor was used in Canada, Australia and France for the study period, the proportion of patients on this drug was low (ranging from 2.6% in France to 4.6% in Australia) and unlikely to explain the survival gap identified. Furthermore, these analyses were conducted prior to the widespread availability of elxacaftor–tezacaftor–ivacaftor. In the future, differential access to CFTR modulators may alter the trajectory of disease and further exacerbate differences in health outcomes in CF. CF communities worldwide need to continue their advocacy efforts to maximise access to all therapies to reduce health disparities such as those identified in this study for individuals living with this disease. For multiple reasons, which will need to be further explored, CF care results in better prognosis in France as compared with Canada and Australia.

CONCLUSION

In conclusion, our study has shown significantly higher survival in France compared with countries with comparable healthcare systems. France survival estimate exceeded 60 years of age which may be due to differences in availability of transplant for those who need it most.

Author affiliations

¹Department of Respiriology, St Michael's Hospital, Toronto, Ontario, Canada

²Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada

³Public Health and Preventative Medicine, Monash University, Clayton, Victoria, Australia

⁴Association Vaincre la Mucoviscidose, Paris, Île-de-France, France

⁵Paediatric Department, Starship Children's Health, Auckland, New Zealand

⁶Paediatrics, Child and Youth Health, The University of Auckland School of Medicine, Auckland, New Zealand

⁷Paediatric Respiratory Department, Starship Children's Health, Auckland, New Zealand

⁸Department of Thoracic Medicine, The Prince Charles Hospital, Cherside, Queensland, Australia

⁹Children's Health Research Centre, The University of Queensland Faculty of Medicine and Biomedical Sciences, Herston, Queensland, Australia

¹⁰Assistance Publique Hôpitaux de Paris, Department of Respiratory Medicine and French Cystic Fibrosis Reference Center, Hôpital Cochin Pneumologie, Paris, Île-de-France, France

¹¹Institut Cochin, Université de Paris, Paris, Île-de-France, France

¹²European Reference Network Respiratory Diseases, Frankfurt, Germany

¹³St Michael's Hospital Li Ka Shing Knowledge Institute, Toronto, Ontario, Canada

¹⁴Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Twitter Scott C Bell @CysFibMD

Acknowledgements We would like to acknowledge and thank all of the patients with CF and families in Canada, Australia, France, New Zealand who consent to be part of their respective national CF patient registries as well as the CF clinic staff who spend many hours inputting the data. Without their efforts, this study would not be possible.

Contributors ALS, SS, PRB, SCB contributed to study concept and design. ALS, RR, LL, CD, JT, CAB contributed to acquisition of data. ALS, SS, PRB, AC, XM, JS, RR, LL, CD, JT, CAB, SCB contributed to analysis and interpretation of data. AC, ALS contributed to drafting of the manuscript. ALS, SS, PRB, AC, XM, JS, RR, LL, CD, JT, CAB, SCB contributed to critical revision of the manuscript for important intellectual content. XM, JS, SS, AC contributed to statistical analysis. ALS, SS, PRB, SCB obtained funding. ALS contributed to study supervision. ALS is the guarantor of the study, therefore accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This study was funded by Cystic Fibrosis Canada (Grant #609767). AC was supported by a Post-Doctoral Fellowship from the Canadian Lung Association.

Disclaimer The study sponsor did not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript; decision to submit the paper for publication.

Competing interests SS is a co-applicant of the CF Canada grant for this study, and received a grant from Vertex pharmaceuticals and the European Respiratory Society, unrelated to this study. SS also received consulting fees from Chiesi pharmaceuticals, unrelated to this study. CAB received support from Cystic Fibrosis New Zealand (for this study) and grants from HRC, Flu Lab and APP, unrelated to this study. CAB was also a trustee for the Bronchiectasis Foundation and chair of the clinical advisory panel for cystic fibrosis as well as the PORT CF NZ registry. PRB received grants from GSK, Vertex and Boehringer Ingelheim, unrelated to this study. PRB has also received consulting fees from Astra Zeneca, Chiesi, Insmad and Vertex as well as payment from Astra Zeneca, Chiesi, GSK, Novartis, Pfizer, Vertex and Zambon, unrelated to this study. PRB also received support for attending meetings and/or travels from Astra Zeneca and Zambon, unrelated to this study. SCB is a co-applicant of the CF Canada grant for this study, in addition to receiving grants from the CF Foundation, NHMRC and MRFF, unrelated to this study. SCB was chair of the Data Safety monitoring Board (DSMB) of the Phase IIA/IB RCT Ataxia telangiectasia project and also participated in the DSMB of the RCT Inhaled hypertonic saline in people with bronchiectasis project, unrelated to this study. SCB was also a board member of Health Translation Qld Board, Gallipoli Medical Research Foundation and the European CF Society, unrelated to this study. ALS has received a grant from CF Canada for this study, as well as the CF Foundation and the Canadian institute for Health research, unrelated to this study. ALS received consulting fees from CF Canada (or her role as the Medical Director of the Canadian CF Registry) and payment from Vertex Pharmaceuticals, unrelated to this study. ALS has also participated in the DSMB of Vertex pharmaceuticals and Horizon Pharma, unrelated to this study.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The research ethics board approval for this study was obtained from Unity Health Toronto (REB #17-312) and approval for use of the proposed registry data was granted by Monash University for Australia, Cystic Fibrosis Canada, Vaincre la Mucoviscidose for France, and Cystic Fibrosis New Zealand. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where

the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs

Catherine Ann Byrnes <http://orcid.org/0000-0002-3032-3172>

Scott C Bell <http://orcid.org/0000-0001-8651-7139>

Pierre Regis Burgel <http://orcid.org/0000-0003-0903-9828>

REFERENCES

- McKone EF, Ariti C, Jackson A, et al. Survival estimates in European cystic fibrosis patients and the impact of socioeconomic factors: a retrospective registry cohort study. *Eur Respir J* 2021;58:2002288.
- McCormick J, Mehta G, Olesen HV, et al. Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. *Lancet* 2010;375:1007–13.
- Stephenson AL, Sykes J, Stanojevic S, et al. Survival comparison of patients with cystic fibrosis in Canada and the United States: a population-based cohort study. *Ann Intern Med* 2017;166:537–46.
- Sykes J, Stanojevic S, Goss CH, et al. A standardized approach to estimating survival statistics for population-based cystic fibrosis registry cohorts. *J Clin Epidemiol* 2016;70:206–13.
- Jackson AD, Goss CH. Epidemiology of CF: how registries can be used to advance our understanding of the CF population. *J Cyst Fibros* 2018;17:297–305.
- Corey M, McLaughlin FJ, Williams M, et al. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41:583–91.
- Stephenson AL, Ramos KJ, Sykes J, et al. Bridging the survival gap in cystic fibrosis: an investigation of lung transplant outcomes in Canada and the United States. *J Heart Lung Transplant* 2021;40:201–9.
- Aaron SD, Stephenson AL, Cameron DW, et al. A statistical model to predict one-year risk of death in patients with cystic fibrosis. *J Clin Epidemiol* 2015;68:1336–45.
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-Ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
- Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. Cdc growth charts: United States. *Adv Data* 2000;1–27.
- Cole TJ, Bellizzi MC, Flegal KM, et al. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;320:1240–3.
- Mahenthalingam E, Baldwin A, Dowson CG. Burkholderia cepacia complex bacteria: opportunistic pathogens with important natural biology. *J Appl Microbiol* 2008;104:1539–51.
- Rubin DB. Multiple imputation after 18+ years. *J Am Stat Assoc* 1996;91:473–89.
- Team RC. R: a language and environment for statistical computing. R foundation for statistical computing. 2012. Available: <http://www.R-project.org/>
- Stanojevic S, Vukovojac K, Sykes J, et al. Projecting the impact of delayed access to elxacaftor/tezacaftor/ivacaftor for people with cystic fibrosis. *J Cyst Fibros* 2021;20:243–9.
- Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. cystic fibrosis inhaled tobramycin Study Group. *N Engl J Med* 1999;340:23–30.
- Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA* 2003;290:1749–56.
- Orsini B, Sage E, Olland A, et al. High-emergency waiting list for lung transplantation: early results of a nation-based study. *Eur J Cardiothorac Surg* 2014;46:e41–7. discussion e47.
- Coriati A, Sykes J, Lemonnier L, et al. Impact of a high emergency lung transplantation programme for cystic fibrosis in France: insight from a comparison with Canada. *Eur Respir J* 2022;59:2100014.
- Audrézet MP, Munck A, Scotet V, et al. Comprehensive CFTR gene analysis of the French cystic fibrosis screened newborn cohort: implications for diagnosis, genetic counseling, and mutation-specific therapy. *Genet Med* 2015;17:108–16.
- Lilley M, Christian S, Hume S, et al. Newborn screening for cystic fibrosis in Alberta: two years of experience. *Paediatr Child Health* 2010;15:590–4.
- Waters DL, Wilcken B, Irwing L, et al. Clinical outcomes of newborn screening for cystic fibrosis. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F1–7.
- Wesley AW, Smith PA, Elliott RB. Experience with neonatal screening for cystic fibrosis in New Zealand using measurement of immunoreactive trypsinogen. *Aust Paediatr J* 1989;25:151–5.
- Tanaka T, Okamoto S, Canning D. National health spending, health-care resources, service utilization, and health outcomes. *Am J Epidemiol* 2022;191:386–96.
- Stukel TA, Fisher ES, Alter DA, et al. Association of hospital spending intensity with mortality and readmission rates in Ontario hospitals. *JAMA* 2012;307:1037–45.

Medjournal

A sua editora de revistas médicas.

Visite www.medjournal.pt para estar a par das nossas publicações e faça o seu registo gratuitamente.

BMJ



Explore our BMJ podcasts
for exclusive extras

Get insights on the latest interviews, debates
and discussions in your specialty

For more information visit
podcasts.bmj.com

Open Access at BMJ

Sharing knowledge and expertise
to create a healthier world



At BMJ we actively champion open access to drive
greater and faster impact for researchers and
healthcare professionals

Publishing open access with us means

Global visibility: Indexing in databases such as PubMed and Web of Science ensures your research is easy to find and cite

Prestige: Our journals are recognised through the trusted BMJ brand, many are affiliated with reputable societies

Quality: Our international editorial boards ensure rigorous peer review and the highest scientific publishing standards

Impact: We publish some of the world's most influential research, with nearly half of our indexed journals ranking within the top 10 of their category



"All components of the publishing experience were among the best I have ever experienced. Peer review and copy-editing were outstanding in quality, speed and responsiveness."

Prof. Till Bärnighausen
Director, Heidelberg Institute of
Global Health (HIGH), Germany



Find out more:

bmj.com/company/open-access-for-authors