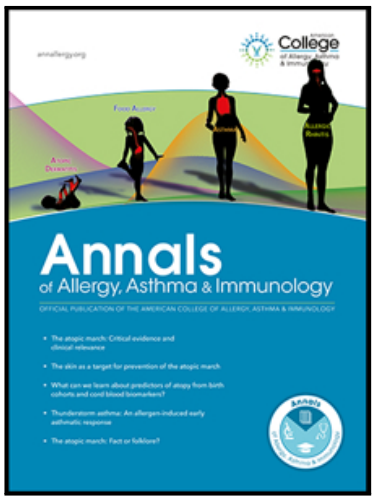
Journal Pre-proof



Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry

Ghislaine Scelo PhD , Carlos A Torres-Duque MD ,
Jorge Maspero PhD , Trung N. Tran MD, PhD , Ruth Murray PhD ,
Neil Martin MD, PhD , Andrew N. Menzies-Gow PhD, FRCP ,
Mark Hew PhD, FRACP , Matthew J. Peters PhD ,
Peter G. Gibson MBBS, FRACP ,
George C. Christoff MD, MPH, PhD , Todor A Popov MD, PhD ,
Andréanne Côté MD, MSc, FRCPC ,
Celine Bergeron MD, FRCPC, MSc , Delbert Dorscheid MD, PhD ,
J. Mark FitzGerald MD, FRCPC , Kenneth R. Chapman MD ,
Louis Philippe Boulet MD FRCPC ,
Mohit Bhutani MD, FRCPC, FCCP , Mohsen Sadatsafavi MD, PhD ,
Libardo Jiménez-Maldonado MD , Mauricio Duran-Silva MD ,
Bellanid Rodriguez BSc , Carlos Andres Celis-Preciado MD, MSc ,
Diana Jimena Cano-Rosales MD , Ivan Solarte MD, MHPE ,
Maria Jose Fernandez-Sanchez MD, MSc ,
Patricia Parada-Tovar BSc , Anna von Bülow MD, PhD ,
Anne Sofie Bjerrum MD, PhD , Charlotte S. Ulrik MD, DMSc ,
Karin Dahl Assing MD , Linda Makowska Rasmussen MD, PhD ,
Susanne Hansen PhD , Alan Altraja MD, PhD ,
Arnaud Bourdin MD, PhD , Camille Taille MD, PhD ,
Jeremy Charriot MD, PhD , Nicolas Roche MD, PhD ,
Andriana I. Papaioannou MD, PhD ,
Konstantinos Kostikas MD, PhD ,
Nikolaos G. Papadopoulos MD, PhD, FRCP ,
Sundeep Salvi MD, PhD , Deirdre Long RGN, RANP, MSc ,
Patrick D. Mitchell MD MRCPI , Richard Costello MB, MD, FRCPI ,
Concetta Sirena PhD , Cristina Cardini MD ,
Enrico Heffler MD, PhD , Francesca Puggioni MD ,
Giorgio Walter Canonica MD , Giuseppe Guida MD, PhD ,
Takashi Iwanaga MD, PhD , Mona Al-Ahmad MBBCh FRCPC ,
Désirée Larenas Linnemann MD, FAAAAI, Dist.Intl.FACAAI ,
Ulises García MD , Piotr Kuna MD, PhD ,
João A. Fonseca MD, PhD , Riyad Al-Lehebi MD, FRCPC ,
Mariko Koh Siyue MBBS, MRCP (UK), FCCP ,
Chin Kook Rhee MD,PhD , Borja G. Cosio MD,PhD ,
Luis Perez de Llano MD, PhD ,
Diahn-Warng Perng (Steve) MD, PhD ,
Erick Wan-Chun Huang MD, PhD , Hao-Chien Wang MD, PhD ,
Ming-Ju Tsai M.D, PhD , Bassam Mahboub MD ,
Laila Ibraheem Jaber Salameh PhD , David Jackson MRCP PhD ,
John Busby PhD , Liam G. Heaney MD ,
Paul Pfeffer MRCP(UK), PhD , Amanda Grippen Goddard DO ,
Eileen Wang MD, MPH , Flavia Hoyte MD ,
Michael E. Wechsler MD , Nicholas Chapman DO ,
Rohit Katial MD , Victoria Carter BSc ,
Lakmini Bulathsinhala MPH , Neva Eleangovan BSc ,

Con Ariti MSc , Juntao Lyu PhD , David Price FRCGP ,
Celeste Porsbjerg MD, PhD

PII: S1081-1206(23)00630-0
DOI: https://doi.org/10.1016/j.anai.2023.08.021
Reference: ANAI 4431

To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 1 June 2023
Revised date: 6 August 2023
Accepted date: 12 August 2023

Please cite this article as: Ghislaine Scelo PhD , Carlos A Torres-Duque MD , Jorge Maspero PhD , Trung N. Tran MD, PhD , Ruth Murray PhD , Neil Martin MD, PhD , Andrew N. Menzies-Gow PhD, FRCP , Mark Hew PhD, FRACP , Matthew J. Peters PhD , Peter G. Gibson MBBS, FRACP , George C. Christoff MD, MPH, PhD , Todor A Popov MD, PhD , Andréanne Côté MD, MSc, FRCPC , Celine Bergeron MD, FRCPC, MSc , Delbert Dorscheid MD, PhD , J. Mark FitzGerald MD, FRCPC , Kenneth R. Chapman MD , Louis Philippe Boulet MD FRCPC , Mohit Bhutani MD, FRCPC, FCCP , Mohsen Sadatsafavi MD, PhD , Libardo Jiménez-Maldonado MD , Mauricio Duran-Silva MD , Bellanid Rodriguez BSc , Carlos Andres Celis-Preciado MD, MSc , Diana Jimena Cano-Rosales MD , Ivan Solarte MD, MHPE , Maria Jose Fernandez-Sanchez MD, MSc , Patricia Parada-Tovar BSc , Anna von Bülow MD, PhD , Anne Sofie Bjerrum MD, PhD , Charlotte S. Ulrik MD, DMSc , Karin Dahl Assing MD , Linda Makowska Rasmussen MD, PhD , Susanne Hansen PhD , Alan Altraja MD, PhD , Arnaud Bourdin MD, PhD , Camille Taille MD, PhD , Jeremy Charriot MD, PhD , Nicolas Roche MD, PhD , Andriana I. Papaioannou MD, PhD , Konstantinos Kostikas MD, PhD , Nikolaos G. Papadopoulos MD, PhD, FRCP , Sundeep Salvi MD, PhD , Deirdre Long RGN, RANP, MSc , Patrick D. Mitchell MD MRCPI , Richard Costello MB, MD, FRCPI , Concetta Sirena PhD , Cristina Cardini MD , Enrico Heffler MD, PhD , Francesca Puggioni MD , Giorgio Walter Canonica MD , Giuseppe Guida MD, PhD , Takashi Iwanaga MD, PhD , Mona Al-Ahmad MBBCh FRCPC , Désirée Larenas Linnemann MD, FAAAAI, Dist.Intl.FACAAI , Ulises García MD , Piotr Kuna MD, PhD , João A. Fonseca MD, PhD , Riyad Al-Lehebi MD, FRCPC , Mariko Koh Siyue MBBS, MRCP (UK), FCCP , Chin Kook Rhee MD,PhD , Borja G. Cosio MD,PhD , Luis Perez de Llano MD, PhD , Diahn-Warng Perng (Steve) MD, PhD , Erick Wan-Chun Huang MD, PhD , Hao-Chien Wang MD, PhD , Ming-Ju Tsai M.D, PhD , Bassam Mahboub MD , Laila Ibraheem Jaber Salameh PhD , David Jackson MRCP PhD , John Busby PhD , Liam G. Heaney MD , Paul Pfeffer MRCP(UK), PhD , Amanda Grippen Goddard DO , Eileen Wang MD, MPH , Flavia Hoyte MD , Michael E. Wechsler MD , Nicholas Chapman DO , Rohit Katial MD , Victoria Carter BSc , Lakmini Bulathsinhala MPH , Neva Eleangovan BSc , Con Ariti MSc , Juntao Lyu PhD , David Price FRCGP , Celeste Porsbjerg MD, PhD , Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry, *Annals of Allergy, Asthma Immunology* (2023), doi: https://doi.org/10.1016/j.anai.2023.08.021

Analysis of comorbidities and multimorbidity in adult patients in the International Severe Asthma Registry

Ghislaine Scelo, PhD[1,2], Carlos A Torres-Duque, MD[3,4], Jorge Maspero, PhD[5], Trung N Tran, MD, PhD[6], Ruth Murray, PhD[2], Neil Martin, MD, PhD[6,7], Andrew N Menzies-Gow, PhD, FRCP[8,9], Mark Hew, PhD, FRACP[10,11], Matthew J Peters, PhD[12], Peter G Gibson, MBBS, FRACP[13,14], George C Christoff, MD, MPH, PhD[15], Todor A Popov, MD, PhD[16], Andréanne Côté MD, MSc, FRCPC[17], Celine Bergeron, MD, FRCPC, MSc[18], Delbert Dorscheid, MD, PhD[19], J Mark FitzGerald†, MD, FRCPC[20], Kenneth R.Chapman, MD[21], Louis Philippe Boulet, MD FRCPC[22], Mohit Bhutani, MD, FRCPC, FCCP[23], Mohsen Sadatsafavi, MD, PhD[24], Libardo Jiménez-Maldonado, MD[4,25], Mauricio Duran-Silva, MD[25], Bellanid Rodriguez, BSc[26], Carlos Andres Celis-Preciado, MD, MSc[27,28], Diana Jimena Cano-Rosales, MD[26], Ivan Solarte, MD, MHPE[27,28], Maria Jose Fernandez-Sanchez, MD, MSc[27,28], Patricia Parada-Tovar, BSc[3], Anna von Bülow MD, PhD[29], Anne Sofie Bjerrum, MD, PhD[30], Charlotte S Ulrik, MD, DMSc[31], Karin Dahl Assing, MD[32], Linda Makowska Rasmussen MD, PhD[33], Susanne Hansen, PhD[34,35], Alan Altraja, MD, PhD[36], Arnaud Bourdin, MD, PhD[37], Camille Taille, MD, PhD[38], Jeremy Charriot, MD, PhD[37], Nicolas Roche, MD, PhD[39], Andriana I Papaioannou, MD, PhD[40], Konstantinos Kostikas, MD, PhD[41], Nikolaos G Papadopoulos, MD, PhD, FRCP[42,43], Sundeep Salvi, MD, PhD[44], Deirdre Long, RGN, RANP, MSc[45], Patrick D Mitchell, MD MRCPI[46], Richard Costello, MB, MD, FRCPI[47], Concetta Sirena, PhD[48], Cristina Cardini MD[48], Enrico Heffler, MD, PhD[49,50], Francesca Puggioni, MD[49], Giorgio Walter Canonica, MD[49,50], Giuseppe Guida, MD, PhD[51], Takashi Iwanaga, MD, PhD[52], Mona Al-Ahmad, MBBCh FRCPC[53], Désirée Larenas Linnemann, MD, FAAAAI, Dist.Intl.FACAAI[54], Ulises García, MD[55], Piotr Kuna, MD, PhD[56], João A Fonseca, MD, PhD[57], Riyad Al-Lehebi, MD, FRCPC[58,59], Mariko Koh Siyue, MBBS, MRCP (UK), FCCP[60], Chin Kook Rhee, MD, PhD[61], Borja G Cosio, MD, PhD[62], Luis Perez de Llano, MD, PhD[63], Diahn-Warng Perng (Steve), MD, PhD[64, 65], Erick Wan-Chun Huang, MD, PhD[66], Hao-Chien Wang, MD, PhD[67], Ming-Ju Tsai, M.D, PhD[68,69], Bassam Mahboub, MD[70], Laila Ibraheem Jaber Salameh, PhD[71], David Jackson, MRCP PhD[72], John Busby, PhD[73], Liam G Heaney, MD[74], Paul Pfeffer, MRCP(UK), PhD[75,76], Amanda Grippen Goddard, DO[77], Eileen Wang, MD, MPH[78], Flavia Hoyte, MD[78], Michael E Wechsler, MD[79], Nicholas Chapman, DO[80], Rohit Katial, MD[78], Victoria Carter, BSc[1,2], Lakmini Bulathsinhala, MPH[1,2], Neva Eleangovan, BSc[1,2], Con Ariti, MSc[1,2], Juntao Lyu, PhD[81], David Price, FRCGP[1,2,82] and, Celeste Porsbjerg, MD, PhD[83].

† Post-humous author

Affiliations

[1]Observational and Pragmatic Research Institute, Singapore, Singapore; [2]Optimum Patient Care Global, Cambridge, UK; [3]CINEUMO, Respiratory Research Center, Fundación Neumológica Colombiana, Bogotá, Colombia; [4]Universidad de La Sabana, Chia, Colombia; [5]Clinical Research for Allergy and Respiratory Medicine, CIDEA Foundation, Buenos Aires, Argentina; [6]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [7]University of Leicester, Leicester, UK; [8]AstraZeneca, Cambridge, UK; [9]Royal Brompton & Harefield Hospitals, London, UK; [10]Allergy, Asthma & Clinical Immunology Service, Alfred Health, Melbourne, Australia; [11]Public Health and Preventive Medicine, Monash University, Melbourne, Australia; [12]Department of Thoracic Medicine, Concord Hospital, Sydney, Australia; [13]Australian Severe Asthma Network, Priority Research Centre for Healthy Lungs, University of Newcastle, Newcastle, Australia; [14]Hunter Medical Research Institute, Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, Australia; [15]Medical University, Sofia, Bulgaria; [16]University Hospital Sv. Ivan Rilski, Sofia, Bulgaria; [17]Department of Medicine, Laval University, Quebec, Canada; [18]Vancouver General Hospital and University of British Columbia, Vancouver, Canada; [19]Center for Heart Lung Innovation, University of British Columbia; [20]Department of Medicine, The University of British Columbia, Vancouver, Canada; [21]University of Toronto, Toronto, Canada; [22]Québec Heart and Lung Institute, Université Laval, Québec City, Canada; [23]Division of Pulmonary Medicine, Department of Medicine, University of Alberta, Alberta, Canada; [24]Respiratory Evaluation Sciences Program, Faculty of Pharmaceutical Sciences, The University of British Columbia; [25]Fundación Neumológica Colombiana, ASMAIRE Program, Bogotá, Colombia; [26]Instituto Neumológico del Oriente, Bucaramanga, Colombia; [27]Pulmonary Unit, Hospital Universitario San Ignacio, Bogota, Colombia; [28]Faculty of Medicine, Pontificia Universidad Javeriana, Hospital Universitario San Ignacio, Bogota, Colombia; [29]Respiratory research unit, Department of Respiratory Medicine and Infectious Diseases, Bispebjerg hospital, Copenhagen, Denmark; [30]Department of Respiratory Medicine and Allergy, Aarhus University Hospital, Denmark; [31]Department of Respiratory Medicine, Copenhagen University Hospital – Hvidovre, Denmark; [32]Department of Respiratory Medicine, Aalborg University Hospital, Aalborg, Denmark; [33]Allergy Clinic, Copenhagen University Hospital-Gentofte, Hellerup, Denmark; [34]Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark; [35]Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; [36]Department of Pulmonology, University of Tartu and Lung Clinic, Tartu University Hospital, Tartu, Estonia; [37]PhyMedExp, Univ Montpellier, CNRS, INSERM, CHU Montpellier, Montpellier, France; [38]Department of Respiratory

Diseases, Bichat Hospital, AP-HP Nord-Université Paris Cité; Paris, France; [39]Department of Respiratory Medicine, APHP-Centre University Paris Cité, Cochin Hospital and Institute (UMR1016), Paris, France; [40]2nd Respiratory Medicine Department, National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece; [41]Respiratory Medicine Department, University of Ioannina, Greece; [42]Division of Infection, Immunity & Respiratory Medicine, University of Manchester, Manchester, UK; [43]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece; [44]Pulmocare Research and Education Foundation, Pune, India; [45]Department of Medicine, Beaumont Hospital, Dublin, Ireland; [46]School of Medicine, Trinity College Dublin, Ireland; [47]Clinical Research Centre, Smurfit Building Beaumont Hospital, Department of Respiratory Medicine, RCSI, Dublin, Ireland; [48]Severe Asthma Network Italy (SANI), Milano, Italy; [49]Personalized Medicine, Asthma and Allergy - IRCCS Humanitas Research Hospital - Rozzano (MI), Italy; [50]Department of Biomedical Sciences - Humanitas University - Pieve Emanuele (MI), Italy; [51]Department of Clinical and Biological Sciences, Severe Asthma and Rare Lung Disease Unit, San Luigi Gonzaga University Hospital, University of Turin, Orbassano, Turin, TO, Italy; [52]Kindai University Hospital, Osakasayama, Japan;[53]Microbiology Department, College of Medicine, Kuwait University, Kuwait, Al-Rashed Allergy Center, Ministry of Health, Kuwait; [54]Centro de Excelencia en Asma y Alergia, Hospital Médica Sur, Ciudad de México, Mexico; [55]Department of Allergy and Immunology, National Medical Center of Bajio, Professor of Allergy and Immunology in the University of Guanajuato, Guanajuato, Mexico; [56]Division of Internal Medicine Asthma and Allergy, Medical University of Lodz, Poland; [57]CINTESIS@RISE, MEDCIDS, Faculty of Medicine of the University of Porto, Porto, Portugal; [58]Department of Pulmonology, King Fahad Medical City, Riyadh, Saudi Arabia; [59]Alfaisal University, Riyadh, Saudi Arabia; [60]Department of Respiratory and Critical Care Medicine, Singapore General Hospital; [61]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [62]Son Espases University Hospital-IdISBa-Ciberes, Mallorca, Spain; [63]Pneumology Service. Lucus Augusti University Hospital. EOXI Lugo, Monforte, Cervo; [64]School of Medicine, National Yang Ming Chiao Tung University; [65]Department of Chest Medicine, Taipei Veterans General Hospital; Taipei, Taiwan; [66]Division of Pulmonary Medicine, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [67]Department of Medicine, National Taiwan University Cancer Center; [68]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [69]School of Medicine, College of Medicine, Department of Internal Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [70]Rashid hospital, Dubai Health Authority (DHA), Dubai, United Arab Emirates; [71]College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; Rashid hospital – Dubai Health Authority (DHA);

[72]Guy's Severe Asthma Centre, Guy's Hospital, King's College London; [73]Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast; [74]Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, UK; [75]Department of Respiratory Medicine, Barts Health NHS Trust, London, UK; [76]Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [77]Allergy Partners of Albuquerque, Albuquerque, NM, USA; [78]Division of Allergy and Clinical Immunology, Department of Medicine, National Jewish Health, Denver, CO, USA; [79]NJH Cohen Family Asthma Institute, Department of Medicine, National Jewish Health, Denver, CO, USA; [80]Saint Joseph Hospital, Denver CO; National Jewish Health, Denver, CO; [81]Griffith University, Centre for Applied Health Economics; [82]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom; [83]Bispebjerg Hospital, Department of Respiratory Medicine and Infectious Diseases, Research Unit.

Corresponding author information

Professor David B Price

Observational and Pragmatic Research Institute

22 Sin Ming Lane, #06 Midview City

Singapore 573969

Tel: +65 3105 1489

Email: dprice@opri.sg

Conflict of Interest Statements

Ghislaine Scelo and **Ruth Murray** are consultants for the Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca.

Carlos A. Torres-Duque has received fees as advisory board participant and/or speaker from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, and Sanofi-Aventis; has taken part in clinical trials from AstraZeneca, Novartis and Sanofi-Aventis; has received unrestricted grants for investigator-initiated studies at Fundacion Neumologica Colombiana from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Grifols and Novartis.

Jorge Maspero reports speaker fees, grants or advisory boards for AstraZeneca, Sanofi, GSK, Novartis, Inmunotek, Menarini, Noucor.

Trung N. Tran, Andrew N. Menzies-Gow and **Neil Martin** is an employee of AstraZeneca and may own stock or stock options in AstraZeneca.

Mark Hew declares grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva, and Seqirus, for unrelated projects.

Matthew J Peters declares personal fees and non-financial support from AstraZeneca and GlaxoSmithKline.

Peter G. Gibson has received speakers and grants to his institution from AstraZeneca, GlaxoSmithKline, Novartis.

George C. Christoff declares no relevant conflicts of interest.

Todor A. Popov declares relevant research support from Novartis and Chiesi Pharma.

Andréanne Côté declares she has received speaking fees and consultant fees from, Sanofi, Regeneron, AstraZeneca, GlaxoSmithKline and ValeoPharma. She received unrestricted grant support from GlaxoSmithKline.

Celine Bergeron reports advisory boards participation of Sanofi, AstraZeneca, Takeda, ValeoPharma and honorarium for presentations for GSK, AstraZeneca, Amgen, Grifols, Sanofi, Regeneron, ValeoPharma

Delbert Dorscheid is on faculty at the University of British Columbia and is supported by the following grants: Canadian Institutes of Health Research, British Columbia Lung Association, and Michael Smith Foundation for Health Research. In addition, he has received speaking fees, travel grants, unrestricted project grants, writing fees and is a paid consultant for Pharma including Sanofi Regeneron, Novartis Canada, AstraZeneca, GlaxoSmithKline and ValeoPharma. He is an active member of Canadian Thoracic Society, American Thoracic Society, European Respiratory Society, and the Allergen Research Network. Delbert Dorscheid does not believe that any of the disclosed potential conflicts represent true conflicts with respect to the information and recommendations included in this manuscript.

J. Mark FitzGerald previously declared grants from AstraZeneca, GSK, Sanofi Regeneron, Novartis paid directly to UBC. Personal fees for lectures and attending advisory boards: AstraZeneca, GSK, Sanofi Regeneron, TEVA.

Kenneth R. Chapman has received grants from Astra Zeneca, Boehringer Ingelheim, Bellus, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Regeneron, Sanofi, Takeda, Vertex, consulting fees from Astra Zeneca, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Sanofi, Takeda. He has leadership or fiduciary role in Alpha-1 Canada, Canadian Thoracic Society, Alpha-1 Foundation.

Louis Phillipe Boulet has received *grants for participation to clinical studies, from* Amgen, AstraZeneca, GlaxoSmithKline, Merck, Novartis, Sanofi-Regeneron, BioHaven, for *Consulting and advisory boards from* Astra Zeneca, Novartis, GlaxoSmithKline, Merck, Sanofi-Regeneron, *and Lecture fees from* AstraZeneca, Covis, Cipla, GlaxoSmithKline, Novartis, Merck, Sanofi.

Mohit Bhutani has received speaker and consultant fees for Astra Zeneca, GSK, Sanofi, Covis, Boerhinger Ingelheim, Valeo.

Mohsen Sadatsafavi has received honoraria from AZ, BI, TEVA, and GSK for purposes unrelated to the content of this manuscript and has received research funding from AZ and BI directly into his research account from AZ for unrelated projects.

Libardo Jiménez-Maldonado has received fees as advisory board participant and/or speaker from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis and Sanofi-Aventis; has participated in clinical trials for AstraZeneca, Novartis and GlaxoSmithKline.

Mauricio Durán-Silva has received fees as advisory board participant and/or speaker from Boehringer-Ingelheim, Novartis, and Sanofi-Aventis; has taken part in clinical trials from AstraZeneca, Novartis, and Sanofi-Aventis.

Bellanid Rodríguez-Cáceres declares no relevant conflict of interest.

Carlos Andrés Celis-Preciado declares no relevant conflict of interest.

Diana Jimena Cano-Rosales reports no conflict of interest.

Ivan Solarte received fees from GSK for participation on Advisory Boards.

Maria Jose Fernandez Sanchez is a part-time employee of GlaxoSmithKline & don´t hold shares in the company.

Patricia Parada-Tovar reports no conflict of interest.

Anna von Bülow reports speakers fees and consultancy fees from AstraZeneca and Novartis, outside the submitted work. She has also attended advisory board for Novartis and AstraZeneca.

Anne-Sofie Bjerrum has received lecture fees from Astra Zeneca, GlaxoSmithKline, Novartis

Charlotte Suppli Ulrik reports personal fees for talks, participation in advisory boards etc. from AZ, GSK, TEVA, BI, Orion Pharma, Sanofi Genzyme, TFF Pharmaceuticals, Covis Pharma, Berlin-Chemie, Takeda, Chiesi and Pfizer outside the submitted work.

Karin Dahl Assing reports no conflict of interest.

Linda M. Rasmussen declares speakers fees from AstraZeneca, Boehringer Ingelheim, TEVA, ALK, and Mundipharma, outside the submitted work and attended advisory board for AstraZeneca, Sanofi and Teva.

Susanne Hansen declares no relevant conflicts of interest.

Alan Altraja has received lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; sponsorships from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, and Sanofi; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi, and Teva.

Arnaud Bourdin has received industry-sponsored grants from AstraZeneca-MedImmune, Boehringer-Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, Sanofi-Regeneron, and consultancies with AstraZeneca-MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi.

Camille Taillé has received lecture or advisory board fees and grants to her institution from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi and Novartis, for unrelated projects.

Jeremy Charriot reports receiving advisory board and lecture fees from AstraZeneca, GlaxoSmithKline, Sanofi and receiving consulting fees for Chiesi, and serving as a trial co-investigator for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sanofi

Nicolas Roche reports grants and personal fees from Austral, Biosency, Boehringer Ingelheim, Novartis, and Pfizer, and personal fees from MSD, GSK, AstraZeneca, Chiesi, Sanofi, Menarini, and Zambon.

Andriana I. Papaioannou has received fees and honoraria from Menarini, GSK, Novartis, Elpen, Boehringer Ingelheim, AstraZeneca, and Chiesi.

Konstantinos Kostikas received honoraria for presentations and consultancy fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, ELPEN, GILEAD, GSK, Menarini, Novartis, Sanofi, Specialty Therapeutics, WebMD. My department has received funding and grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Innovis, ELPEN, GSK, Menarini, Novartis and NuvoAir (paid to the University of Ioannina).

Nikolaos G. Papadopoulos has been a speaker and/or advisory board member for Abbott, Abbvie, ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GSK, HAL, Faes Farma, Medscape, Menarini, MSD, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, Viatris.

Sundeep Salvi declares research support and speaker fees from Cipla, Glenmark, GSK

Deirdre Long declares no conflict of interest.

Patrick D Mitchell has received speaker fees from GlaxoSmithKline, AstraZeneca, Teva and Novartis, and has received grants from AstraZeneca and Teva.

Richard W. Costello has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for GlaxoSmithKline and Novartis, has received grant support from GlaxoSmithKline and Aerogen and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence and prediction of exacerbations.

Concetta Sirena declares no relevant conflicts of interest.

Cristina Cardini declares no relevant conflicts of interest.

Enrico Heffler declares personal fees from: Sanofi, Regeneron, GSK, Novartis, AstraZeneca, Stallergenes, Circassia

Francesca Puggioni reports having received lectures or advisory board fees from: Menarini, Mundipharma, Chiesi, Alk Abello, Astra Zeneca, Boehringer Ingelheim, Guidotti, malesci, glaxo Smith Kline, hal Allergy, Novartis, Sanofi, Regeneron, Stallergenes greer, valeas, Almirall

G. Walter Canonica has received research grants, as well as lecture or advisory board fees from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas.

Takashi Iwanaga received lecture fees from Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim and AstraZeneca.

Mona Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline. Received a grant from Kuwait Foundation for the Advancement of Sciences (KFAS).

Désirée Larenas Linnemann reports personal fees from ALK-Abelló, Astrazeneca national and global, Bayer, Chiesi, Grunenthal, Grin, GSK national and global, Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, Carnot, grants from Abbvie, Bayer, Lilly, Sanofi, Astrazeneca, Pfizer, Novartis, Circassia, UCB, GSK, outside the submitted work.**Ulises Noel Garcia Ramirez** received fees as speaker and advisory board from: AstraZeneca, GSK, Sanofi Genzyme, Chiesi and Novartis

Piotr Kuna reports personal fees from Adamed, AstraZeneca, Berlin Chemie Menarini, FAES, Glenmark, Novartis, Polpharma, Boehringer Ingelheim, Teva, Zentiva, outside the submitted work.

João A Fonseca reports grants from or research agreements with AstraZeneca, Mundipharma, Sanofi Regeneron and Novartis. Personal fees for lectures and attending advisory boards: AstraZeneca, GSK, Mundipharma, Novartis, Sanofi Regeneron and TEVA.

Riyad Al-Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi, and participated in advisory board fees from GlaxoSmithKline, AstraZeneca, Novartis, Abbott

Mariko Siyue Koh reports grant support from AstraZeneca, and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, Astra-Zeneca, Novartis, Sanofi and Boehringer Ingelheim, outside the submitted work.

Chin Kook Rhee received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer.

Borja G. Cosio declares grants from Chiesi and GSK; personal fees for advisory board activities from Chiesi, GSK, Novartis, Sanofi, Teva, and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, GSK, Menarini, and AstraZeneca, outside the submitted work.

Luis Perez-de-Llano reports grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from GSK, grants, personal fees and non-financial support from TEVA, personal fees and non-financial support from Chiesi, grants, personal fees and non-financial support from Sanofi, personal fees from MSD, personal fees from TECHDOW PHARMA, grants, personal fees and non-financial support from FAES, personal fees from Leo-Pharma, grants and personal fees from GEBRO, personal fees from GILEAD, outside the submitted work;

Diahn-Warng Perng (Steve) received sponsorship to attend or speak at international meetings, honoraria for lecturing or attending advisory boards, and research grants from the following companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Daiichi Sankyo, Shionogi, and Orient Pharma

Erick Wan-Chun Huang declares no relevant conflict of interest.

Hao-Chien Wang reports no conflict of interest.

Ming-Ju Tsai has received grants from Boehringer Ingelheim and has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis and Orient EuroPharma.

Bassam Mahboub reports no conflict of interest.

Laila Salameh declares no relevant conflict of interest.

David J. Jackson has received speaker fees and consultancy fees from AZ, GSK, Sanofi Regeneron, BI and research funding from AstraZeneca.

John Busby has received research grants from AstraZeneca and personnel fees from NuvoAir, outside the submitted work.

Liam G. Heaney has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; he has received grants from MedImmune, Novartis UK, Roche/ Genentech Inc, and Glaxo Smith Kline, Amgen, Genentech/Hoffman la Roche, Astra Zeneca, MedImmune, Glaxo Smith Kline, Aerocrine and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK and Napp Pharmaceuticals; he has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen.

Paul E. Pfeffer has attended advisory boards for AstraZeneca, GlaxoSmithKline, and Sanofi; has given lectures at meetings supported by AstraZeneca and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis and Sanofi, for which his institution received remuneration; and has a current research grant funded by GlaxoSmithKline.

Amanda Grippen Goddard reports lecture fees from Sanofi.

Eileen Wang has received honoraria from AstraZeneca, GlaxoSmithKline, and Genentech. She has been an investigator on studies sponsored by AstraZeneca, GlaxoSmithKline, Genentech, Sanofi, Novartis, and Teva, for which her institution has received funding.

Flavia Hoyte declares honoraria from AstraZeneca and Genentech. She has been an investigator on clinical trials sponsored by GlaxoSmithKline, Genentech, Teva, Sanofi, for which her institution has received funding.

Michael E. Wechsler reports grants and/or personal fees from Novartis, Sanofi, Regeneron, Genentech, Sentien, Restorbio, Equillium, Genzyme, Cohero Health, Teva, Boehringer Ingelheim, AstraZeneca, Amgen, GlaxoSmithKline, Cytoreason, Cerecor, Sound biologic, Incyte, Kinaset

Nicholas Chapman reports no conflict of interest.

Rohit Katial declares no relevant conflict of interest.

Victoria Carter is an employee of Optimum Patient Care (OPC). OPC is a co-funder of the International Severe Asthma Registry and an employee of Optimum Patient Care, a co-founder of the APEX-COPD initiative.

Lakmini Bulathsinhala is an employee of the Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca.

Neva Eleangovan was an employee of the Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca.

Con Ariti was an employee of the Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca.

Juntao Lyu was an employee of Optimum Patient Care (OPC). OPC is a co-founder of the International Severe Asthma Registry.

David Price has advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, Thermofisher; funding for patient enrolment or completion of research from Novartis; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care

Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline.

Celeste M. Porsbjerg has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, TEVA, GlaxoSmithKline, ALK, and Sanofi-Genzyme.

Funding Source: This study was conducted by the Observational and Pragmatic Research Institute (OPRI) Pte Ltd and was partially funded by Optimum Patient Care Global and AstraZeneca Ltd. No funding was received by the Observational & Pragmatic Research Institute Pte Ltd (OPRI) for its contribution.

Clinical Trial Registration: The ISAR database has ethical approval from the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218) and is registered with the European Union Electronic Register of Post-Authorization studies (ENCEPP/DSPP/23720). The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) Code of Conduct (EMA 2014; EUPAS44024) and with all applicable local and international laws and regulation, and registered with ENCEPP (https://www.encepp.eu/encepp/viewResource.htm?id=48848). Governance was provided by ADEPT (registration number: ADEPT1121).

Key words: allergic rhinitis; anxiety/depression; chronic obstructive pulmonary disease; chronic rhinosinusitis; diabetes, dyslipidemia; gastroesophageal reflux disease; hypertension; nasal polys; obesity; osteoporosis; sleep apnea

Abbreviations:

ACQ: Asthma Control Questionnaire

ACT: Asthma Control Test

AD: atopic dermatitis

AR: allergic rhinitis

AU: Australia

BEC: blood eosinophil count

Bx: biologic

CA: Canada

CHD: chronic heart disease

CI: confidence interval

COPD: chronic obstructive pulmonary disease

CRS: chronic rhinosinusitis (with or without NP)

CVA: cerebrovascular accident

DK: Denmark

ES: Spain

FEV_1: forced expiratory volume in one second

FeNO: fractional exhaled nitric oxide

GERD: gastro-esophageal reflux disease

GINA: Global Initiative for Asthma

HT: hypertension

IE: Ireland

ISAR: International Severe Asthma Registry

IT: Italy

IgE: immunoglobulin E

JP: Japan

LTOCS: long term oral corticosteroid

$ppFEV_1$: percent predicted forced expiratory volume in one second

MX: Mexico

NP: nasal polyps

OCS: oral corticosteroid

OP: osteoporosis

OR: odds ratio

PE/VTE: pulmonary embolism/venous thromboembolism

PL: Poland

PN: pneumonia

PT: Portugal

SA: sleep apnea

SK: South Korea

TW: Taiwan

UAE: United Arab Emirates

UK: United Kingdom

USA: United States of America

VCD/LS: vocal cord dysfunction/laryngeal spasm

VCD: vocal cord dysfunction

VTE: venous thromboembolism

Manuscript word count: 3996 (max: 4,000)

Figures: 2

Tables: 4

Abstract

Background: Investigation for the presence of asthma comorbidities is recommended by GINA as their presence can complicate asthma management.

Objective: To understand the prevalence and pattern of comorbidities and multimorbidity in adults with severe asthma and their association with asthma-related outcomes.

Methods: This was a cross-sectional study using data from the International Severe Asthma Registry from 22 countries. Thirty comorbidities were identified and categorized a priori as either (1)

potentially T2-related, (2) potentially oral corticosteroid (OCS)-related or (3) mimicking/aggravating asthma. The association between comorbidities and asthma-related outcomes was investigated using multivariable models adjusted for country, age at enrollment, and sex.

Results: Of 11,821 patients, 69%, 67%, and 55% had ≥1 potentially T2-related, potentially OCS-related, or mimicking/aggravating comorbidities, respectively; 57% had ≥3 comorbidities, and 33% had comorbidities in all three categories. Patients with allergic rhinitis (AR), nasal polyposis (NP), and chronic rhinosinusitis (CRS) experienced 1.12- (p=0.003), 1.16- (p<0.001) and 1.29-times (p<0.001) more exacerbations/year, respectively, than those without. Patients with NP and CRS were 40% and 46% more likely (p<0.001), respectively, to have received long-term (LT) OCS. All assessed potential OCS-related comorbidities (except obesity) were associated with greater likelihood of LTOCS use (ORs: 1.23-2.77) and, except for dyslipidemia, with greater likelihood of uncontrolled asthma (ORs: 1.29-1.68). All mimicking/aggravating comorbidities assessed were associated with more exacerbations (1.24-1.68 times more), all (except bronchiectasis) with increased likelihood of uncontrolled asthma (ORs: 1.57-1.81) and all (except COPD) with increased likelihood of LTOCS use (ORs: 1.37-1.57). Greater number of comorbidities was associated with worse outcome.

Conclusion: In a global study, comorbidity or multimorbidity is reported in most adults with severe asthma and is associated with poorer asthma-related outcomes.

Introduction

From 2014, the Global Initiative for Asthma (GINA) has focused on asthma control and personalized management of patients' modifiable risk factors, including comorbidities[1,2] Investigation for the presence of comorbidities is recommended at every part of the asthma management journey, and multimorbidity is recognized as a common problem in patients with asthma.[1] Some of these comorbidities can complicate asthma treatment, significantly increase the risk of poor asthma-related outcomes,[3–5] and are associated with significant productivity losses.[6] Overall comorbidity-attributable healthcare costs are five times higher than costs attributable to asthma alone.[7]

The list of asthma comorbidities is extensive and broadly divided into 3 categories: (i) type 2 inflammatory (T2) comorbidities, (ii) comorbidities potentially related to oral corticosteroid (OCS) exposure and (iii) comorbidities that mimic/aggravate asthma symptoms, with some overlap between categories.[1,8,9] T2 inflammatory comorbidities (eg, allergic rhinitis (AR), chronic rhinosinusitis (CRS), and nasal polyposis (NP)), are markers of T2 inflammation and associated with more severe asthma (eg, particularly CRSwNP). OCS-related comorbidities include obesity, osteoporosis, diabetes, anxiety and depression.[8,10,11] Anxiety and depression are associated with worse asthma symptom control,

reduced medication adherence, and reduced asthma-related quality of life (QoL), and are also sometimes categorized as asthma mimicking/aggravating.[12] Comorbidities that mimic/aggravate asthma symptoms include gastroesophageal reflux disease (GERD) and chronic obstructive pulmonary disease (COPD). GERD is a common cause of dry cough and may be aggravated by the use of asthma medications such as β-agonists and theophylline.[1] COPD can present with asthma, a condition sometimes referred to as asthma-COPD overlap.[13] Asthma COPD overlap is associated with a greater symptom burden, more frequent exacerbations, worse QoL, a more rapid lung function decline, a higher mortality rate, and a greater use of healthcare resources compared to patients with either asthma or COPD alone.[13] Few large-scale studies are published that assessed comorbidities in severe asthma, and little has been reported on the burden and impact of multimorbidity.[14–16]

The International Severe Asthma Registry (ISAR), the largest adult severe asthma registry in the world, including data on >12,000 patients, collects information on comorbidities, asthma clinical characteristics and outcome domains.[17–20] Its size and scope permits an in-depth look at comorbidity prevalence globally and by country, facilitates comorbidity categorization, assessment of presentation patterns, and investigation of the relationship between comorbidities and asthma. The aim of our study was to understand the global prevalence, distribution and co-existence of comorbidities, including multimorbidities, in adults with severe asthma and investigate the association of comorbidities with clinical and asthma-related outcomes.

Methods

Study design and data sources

This was a cross-sectional study using data from ISAR (https://isaregistries.org/), details of which have been described elsewhere.[20] We included data from 22 countries that shared data from (2010-2022) with ISAR (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, United Arab Emirates, UK, and USA). Data were either retrospective (collected pre-ISAR launch [ie, 1 May 2017]) or prospective (collected post-ISAR launch). For patients who did not subsequently initiate biologics, the enrollment date was the visit closest to ISAR launch for retrospectively enrolled patients, and the first visit date for prospectively enrolled patients. For patients who subsequently initiated biologics, the enrollment date was the biologic initiation date for both retrospectively and prospectively enrolled patients. The pre-biologic period was used to avoid confounding potentially caused by biologics on asthma-related outcomes and biomarkers.

This study is exempt from IRB. All ISAR data collection sites have obtained regulatory agreement in compliance with specific data transfer laws, country-specific legislation, and relevant Ethic Committees and organizations (**eAppendix 1**).

Patients

Patients were aged ≥18 years, had severe asthma (ie, receiving treatment at GINA 2018 Step 5 or with uncontrolled asthma at GINA Step 4 (ie, treated with inhaled corticosteroid [ICS]/long-acting β_2-agonist),[21] and had data on ≥1 comorbidity collected as part of this study. We included all eligible patients to assess individual comorbidity prevalence, pre-defined comorbidity categories, and to explore comorbidity co-occurrence (prevalent series). Only prospectively enrolled patients were included in the association analysis (association series), as at the time of the analysis, clinical and

functional endpoint data were scarce for the retrospectively enrolled patients. Patients with missing sex data were excluded from the association analysis.

Comorbidity data collection

Core physician-assessed, clinically diagnosed comorbidities (ie, eczema, AR, CRS, NP, and obesity) were collected by all countries. Additional potentially related OCS comorbidities (maximum 16; eg, circulatory system diseases, ocular diseases) were collected by many countries. Some countries also elected to collect extra comorbidity variables (eg, food allergy, dyslipidemia, GERD) (**Table 1**; **eTable 1**).[20,22]

Study variables

Thirty comorbidities were identified and categorized *a priori* as (1) potentially T2-related, (2) potentially OCS-related, or (3) mimicking/aggravating asthma. These categories were identified by extensive literature search and expert consensus. Because presence/absence information on comorbidities was not always available at each visit, we used all visits available (before or after enrollment) to compute a never/ever present variable for each individual comorbidity. Demographic, clinical characteristics (eg, age of onset, biomarker levels) and pre-biologic asthma-related outcomes were also collected (ie, long-term OCS (LTOCS) use, exacerbation rate, percent predicted forced expiratory volume in one second (ppFEV$_1$),[23] and asthma control). Definitions/categorizations of variables and timing of collection are provided in **Table 2** and **eTable 2**.

Study Outcomes

The prevalence of individual comorbidities (by category and country), multimorbidity (1, 2, and 3+ comorbidities), and comorbidity co-occurrences across categories were calculated. The number of countries collecting information on each type of comorbidity and how these data were collected (eg, categorially, check box, binary field, free text, ICD code) was also assessed. We assessed the association between the most common individual comorbidities (*a priori* threshold prevalence of ≥10%) and the number of comorbidities (overall and by comorbidity category) and demographic characteristics, clinical characteristics, and asthma-related outcomes. Demographic characteristics, clinical characteristics, and asthma-related outcomes were assessed at the time of enrollment.

Statistics

The statistical analysis plan was predefined. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct all statistical analyses.[24] Descriptive statistics were used to summarize comorbidity prevalence (individual and co-occurrences). For individual comorbidities, the denominator was computed as the number of patients with presence/absence information available on at least one visit (**eAppendix 1**). Comorbidity co-occurrence was assessed in patients with non-missing data for at least 3 comorbidities and described as the prevalence of 1, 2, and ≥3 comorbidities, overall and by categories.

The prevalence of comorbidities by demographic characteristics was compared through univariate analysis. The association between clinical characteristics/asthma-related outcomes and comorbidities were assessed through multivariable models. For the association of individual comorbidity with outcome, comorbidity (ever/never present) was the explanatory variable and clinical characteristics/asthma-related outcomes were the dependent variables. For the association between the number of comorbidities and outcomes, we used ordinal variables (0, 1, 2, or 3+ comorbidities), overall and within comorbidity categories. All models were adjusted for country, age at registry

enrollment, and sex. For continuous dependent variables (age at asthma onset, biomarkers, and $ppFEV_1$), we used linear regression, and results were expressed as differences in means comparing patients with to those without the considered comorbidity. For binary dependent variables (LTOCS use [yes/no] and asthma control [uncontrolled/partly or well controlled]), we used logistic regressions, and results were expressed as odds ratios (ORs). The comorbidity/exacerbation rate association was investigated using negative binomial regressions. All comparisons were two-sided and significance considered at an α level of 0.05. Additional details on all statistical analyses are provided in the **eAppendix 1**.

Results

Subject disposition and baseline characteristics

As of 24 January 2022, ISAR contained data from 22 countries including 12,099 adult patients with severe asthma (**eFigure 1**). A total of 11,821 patients were included in the prevalence series, and 8499 in the association series. Patients in both assessment cohorts were predominantly female (62%), aged 50-69 years at enrolment (50%), had later onset asthma (ie, aged ≥12 yrs: ~80%) an eosinophilic phenotype (~87%), and evidence of atopy (>60%) (**eTables 3A & 3B**). Baseline characteristics for both series are provided in the eSupplement (**eTable 3A & 3B**).

omorbidity data collection

Information on comorbidities was not uniformly collected by countries, depending upon whether the comorbidity was core, additional, or extra (**Table 1**). Most potentially T2-related and OCS-related comorbidities were consistently collected. However, not all countries collected information on urticaria (collected in 4 countries), food allergy (n=5), aspirin sensitivity (n=7), eosinophilic esophagitis (n=3), hypertension (n=12), dyslipidemia (n=4), and adrenal insufficiency (n=3). Comorbidities mimicking/aggravating asthma symptoms were all infrequently collected (eg, GERD, COPD, and bronchiectasis were each collected by only 7 countries) (**Table 1**).

Comorbidity information was collected in different ways (eg, as categorical [eg, current/past/never] or binary [yes/no] data, or using check boxes, free text, or ICD codes from electronic medical records), and there was inter-category variability in method of collection (**eFigure 2**). Potentially T2-related comorbidity information was gathered categorically, predominantly (**eFigure 2A**), whereas method of collection for potentially OCS-related comorbidities varied by comorbidity – collected mostly as categorical/binary data for sleep apnea, anxiety/depression, and osteoporosis, and as free text for hypertension (**eFigure 2B**). Methods of collection for comorbidities mimicking/aggravating asthma symptoms showed the greatest heterogeneity (**eFigure 2C**).[17]

Prevalence of comorbidities

Individual comorbidities

Patients with severe asthma had a wide range of comorbidities. The most prevalent reported individual comorbidities were AR (49%; n=5525/11,281), CRS (46%; n=5151/11,223), obesity (42%; n=4893/11,583), and GERD (44%; n=3243/7400) (**Table 1**). Of 3,745 patients with reported AR and available data on allergen tests (skin prick test or serum tests), 746 (19.9%) were not positive to any tested allergen. Additionally, marked between-country variation was noted for each of these comorbidities (**eFigure 3**). Reported AR prevalence ranged from 4.6% in the UK to 92.9% in Mexico, obesity prevalence ranged from 9.3% in South Korea to 64.2% in Kuwait, and GERD prevalence ranged from 3.4% in the UK to 56.8% in the USA.

Comorbidity categories

Overall, the prevalence of at least one comorbidity was 92%. The estimates for ≥1 potentially T2-related comorbidity, ≥1 potentially OCS-related comorbidity, and ≥1 comorbidity mimicking/aggravating asthma were 69%, 67%, and 55%, respectively. These estimates were relatively stable in sensitivity analysis restricting the study population to patients with various thresholds of minimum numbers of comorbidities with available data (**eTable 4**).

Comorbidity counts and multimorbidity

Most patients (57.3%; n=6761/11,794) had at least 3 comorbidities of any type (**Figure 1**). Of note, 39.5% (n=4600/11,623) of patients had ≥2 potentially T2-related comorbidities, 39.9% (n=4589/11,489) had ≥2 potentially OCS-related comorbidities, and 20.9% (n=1567/7496) had ≥2 comorbidities mimicking/aggravating asthma **(Figure 1)**. These proportions were relatively stable when explored by subgroups of patients with increasing numbers of comorbidities with available data (**eTable 5**). In a subpopulation of 7,561 patients who had information available for ≥1 comorbidity in each category, 2,477 (32.8%) had comorbidities in all three categories. We further explored the most frequent comorbidities and comorbidity combinations by number (1, 2, or ≥3) of reported

comorbidities (**eTable 6**). The most common dual comorbidity patterns in patients with two reported comorbidities were AR and CRS (44.8%), obesity and sleep apnea (21.7%), and GERD and COPD (32.6%), for potentially T2-related, potentially OCS-related, and comorbidities mimicking/aggravating asthma symptom categories, respectively.

Comorbidity associations with demographic characteristics, biomarkers, and asthma outcomes

We focused on the 15 most common comorbidities (prevalence ≥10%) with restriction to prospectively enrolled patients (n=8499; patient characteristics available in **eTable 3B**). The association of comorbidities with sex, age, and smoking status is provided in the eSupplement (**eTables 7-9**). The presence of comorbidities was significantly associated with asthma clinical characteristics and outcomes, and the pattern of the association was comorbidity-dependent (**Table 3; eTables 10-17; Figure 2**).

Biomarkers and age at asthma onset

Patients with potentially T2-related comorbidities had higher biomarker concentrations than those without (**Table 3; eTables 11-13**). Patients with CRS and NP had higher BEC and higher FeNO concentrations, patients with AR had higher concentrations of all three biomarkers, and those with eczema/AD had higher IgE concentrations. By contrast, potentially OCS-related comorbidities were either not associated with this biomarker concentration elevation or were associated with lower concentrations, with the exception of osteoporosis, which was associated with elevated BEC (**Table 3; eTable 11**). Comorbidities mimicking/aggravating asthma symptoms were also not associated with biomarker concentration elevation, with the exception of bronchiectasis, which was associated with elevated BEC and IgE (**Table 3; eTables 11 & 12**).

A few comorbidities were associated with age at asthma onset (**Table 3; eTable 10**). Patients with AR, eczema/AD, and diabetes were on average younger at asthma onset than patients without, whereas patients with CRS and NP were on average older at asthma onset.

Individual comorbidities and asthma outcomes

Having a comorbidity was generally associated with receiving LTOCS and with higher exacerbation rates, with a variable impact noted on lung function and asthma control (**Figure 2 A-D; eTables 14-17**). However, the extent of comorbidity association on asthma outcome was also comorbidity-dependent.

Potentially T2-related comorbidities

CRS was associated with a poorer outcome for 2 variables: exacerbations and LTOCS use. Compared to those without CRS, patients with comorbid CRS had 29% more exacerbations and were 46% more likely to receive LTOCS (**eTables 14 & 15)**. NP was also associated with a poorer outcome for these 2 variables. AR was associated with higher exacerbation rates only, and AD was not associated with a significantly poorer asthma outcome for any variable assessed (**Figure 2A-D**). None of these potentially T2-related comorbidities were associated with poorer lung function, compared to those without; indeed, some of them were associated with better lung function (ie, AR, CRS, and NP) (**eTable 16)**. Additionally, none of these T2-related comorbidities were significantly associated with poorer asthma control **(eTable 17**).

Potentially non-T2-related comorbidities

Having hypertension or osteoporosis was associated with a significantly worse outcome in each of the four asthma outcomes assessed. Patients with osteoporosis were over twice as likely to have used LTOCS (OR 2.77; 95% CI: 2.35, 3.27; **eTable 14**) and experienced 61% more exacerbations (95% CI: 45%, 79%) than those without osteoporosis (**Figure 2A; eTable 15**). Overall, 9 out of 11 non-T2-related comorbidities were associated with higher odds of LTOCS use, and 8 out of 11 were associated with higher exacerbation rates.

Most of the comorbidities that were potentially OCS-related or mimicking/aggravating asthma symptoms were also associated with worse asthma control. This was particularly the case for sleep apnea (OR 1.59; 95% CI 1.32, 1.92), anxiety/depression (OR 1.68; 95% CI 1.40, 2.02), GERD (OR 1.81;

95% CI 1.48, 2.23), and vocal cord dysfunction (VCD)/laryngeal spasm (OR 1.81; 95% CI 1.38, 2.37) (**Figure 2D; eTable 17**). Some of them were also associated with worse lung function, particularly, COPD (-15.9 $ppFEV_1$) and bronchiectasis (-5.24 $ppFEV_1$) (**Figure 2C; eTable 16**).

Number of comorbidities and asthma outcomes

Patients with a greater number of comorbidities, both overall and for each comorbidity category, had worse asthma outcomes, with the exception of $ppFEV_1$ and asthma control for potentially T2-related comorbidities (**Table 4**).

Discussion

Our study is the first global analysis of comorbidity burden in patients with severe asthma, in terms of both prevalence and association with asthma clinical characteristics and outcomes. It included an in-depth exploration by category, multimorbidity, and co-occurrence patterns across categories, and investigated the extent and method of comorbidity information collection; a reflection of the complexity of comorbidity presentation and reporting in real-life. We found a differential association between comorbidities and asthma biomarkers, a comorbidity-specific association across multiple asthma outcomes and a clear relationship between number of comorbidities and extent of outcome impairment. Having CRS and NP, in particular, was associated with more exacerbations and LTOCS use, whereas poor asthma control was associated with all potentially OCS-related comorbidities (with the exception of dyslipidemia). LTOCS use was associated with the largest number of comorbidities across the spectrum.

Patients with severe asthma presented with a wide variety of comorbidities, with some more prevalent than others (eg, AR, obesity, and GERD); more than 50% of patients with severe asthma had 3 or more comorbidities. Appropriate management of these multimorbid patients may be challenging due to the need for a multidisciplinary approach that may not be available in all countries. There also was marked inter-country variability in comorbidity prevalence estimates, possibly due to current gaps

in comorbidity reporting, heterogeneity in reporting methodology, misclassification (e.g. NAR many have been captured within the AR category), and/or inter-country demographic variability.[25] Although all countries collected the ISAR comorbidity core variables (ie AR, CRS, NP, AD, and obesity) and many also collected the optional OCS-related comorbidities,[22] collection gaps were noted for certain T2-related comorbidities (eg, urticaria, food allergy, aspirin sensitivity, and eosinophilic esophagitis) and some OCS-related comorbidities (eg, sleep apnea, hypertension, dyslipidemia, and adrenal insufficiency). Additionally, the majority of countries did not collect (or did not report) information on comorbidities mimicking/aggravating asthma symptoms, likely as these variables were not part of the original Delphi-agreed ISAR variables.[17] We also noted marked variation in how comorbidity information was recorded. These findings emphasize the need to focus on comorbidity assessment in clinical care, particularly those that are OCS-related considering the adverse event and socioeconomic impact associated with their use[10,26,27], as well as the need for a 'clinical protocol' to guide assessment and management of severe asthma, and standardized tools to collect and report comorbidity data.

The position of T2-related comorbidities as drivers of continued exacerbations and their association with poor asthma control is well documented.[5,28,29] For example, among patients with asthma in UK primary care, those with 1 or 2 potentially T2-related comorbidities were significantly less likely to achieve asthma control (ORs: 0.95 and 0.86, respectively) compared to those without [5] In our study, we noted higher exacerbation rates for those with comorbid AR, CRS, or NP and higher odds of LTOCS use for those with comorbid CRS and NP than those without; these results have been confirmed by others, albeit at the national level and not specifically in severe asthma.[30,31] However, we additionally found a marked cumulative negative effect of multiple T2-related comorbidities on exacerbation rate and LTOCS use that has not previously been reported; this is particularly important when one considers that approximately 40% of patients had ≥2 physician-assessed potentially T2-related comorbidities. The positive association noted in our study between nasal T2-comorbidies and lung function may be due to earlier diagnosis of asthma in these patients (as the association between these

comorbidities and asthma is well documented),[32] earlier therapy intervention that may blunt lung function decline, and/or improved responsiveness to ICS in T2-high asthma.[33,34]

Mindful of the serious long-term adverse effects of OCS, GINA 2023 urges physicians to consider maintenance OCS as a "last resort" if other treatments have been optimized and no alternative is available.[1] However, globally some 20 to 60% of patients with severe asthma are still treated with LTOCS.[35] We found that 68% and 40% of patients had ≥1 and ≥2 potentially OCS-related comorbidities, respectively. Others have reported higher prevalence rates of conditions linked to OCS use in patients with severe asthma (93%), even in those with mild/moderate disease (78%).[11] Reassuringly, we found a strong association between potentially OCS-related comorbidities and LTOCS use at enrollment. Although our cross-sectional design prevents an assumption of any directional relationship, it is probable that LTOCS exposure caused the occurrence of comorbidities, a hypothesis strengthened by the greater odds of LTOCS use with greater number of OCS-related comorbidities. Furthermore, the presence of an OCS-related comorbidity was generally associated with higher exacerbation rates and higher odds of uncontrolled asthma, with higher rates and odds noted with increasing number of comorbidities. Others have reported an association between obesity, anxiety/depression, and diabetes and increased risk of experiencing multiple exacerbations,[36] as well as sleep apnea and poor asthma control, even in subjects who used their inhalers correctly.[37] Taken together, these results highlight the need for OCS stewardship to regulate OCS use.[38] A recently published expert consensus agreed that OCS use should be minimized, that OCS tapering should be attempted in every patient, that biological therapies are useful OCS-sparing agents, and that patients should be systematically assessed for suitability for biological therapy.[39]

Comorbidities mimicking/aggravating asthma were also relatively common in our study, with a strong association noted between these comorbidities and LTOCS use. The presence of COPD, GERD, and VCD/laryngeal spasms was also associated with significantly greater odds of having poorly controlled disease and higher exacerbation rates. Other studies have found that patients with comorbid GERD

were 3 times more likely to have uncontrolled asthma than their counterparts without GERD,[40] that these patients experienced 1.6 times more exacerbations/year,[41] and that GERD was predictive of future multiple exacerbations.[36] These results highlight the importance of a thorough comorbidity assessment in order to differentiate severe from poorly controlled disease caused by comorbidities, to treat the cause and not the symptoms, and to prevent inappropriate treatment and inadequate response.

Missing data were a limitation of our study - clinical variables were not available for all patients, particularly spirometry data during the Covid-19 pandemic. However, sensitivity analyses excluding patients with fewer collected comorbidities led to estimates of similar magnitudes, and sample sizes for all outcome measures were still large. In line with ISAR's current inclusion criteria, data were also not captured for those aged <18 years, although in the future, we hope to include children and adolescents in ISAR with the view of capturing the entire asthma life cycle. Although we included a long list of comorbidities, this was not exhaustive. Non-allergic rhinitis (NAR) was not included, for example, although NAR may have been included in the AR categorization by some countries, evidenced by the fact that 19.9% of patients with reported AR were not positive to any tested allergen. Additionally, information regarding comorbidity severity was not collected, results may have been confounded by asthma severity and phenotype, and there may have been some selection bias on the biomarkers collected. There was also marked inter-country variability in how comorbidity data were collected (although no clear pattern by data source was observed) and wide inter-country variability in the prevalence of certain comorbidities. The range of AR prevalence was particularly wide, lowest in the UK and highest in Mexico (e-Figure 3). This may have been due to under-reporting in the former, and almost excusive collection of data from allergist centers in the latter. Furthermore, although inclusion of highly selective patients in some countries (eg, UK and Denmark), may have positively selected for patients with multiple comorbidities, this is not true for all, and analyses were adjusted for country. The data incompleteness inherent to real-world studies and the heterogeneity in data collection inherent to international studies led us to harmonize information on comorbidity into

"ever/never present" variables using data available from all visits. Despite maximizing data on comorbidities, this compromise might have diluted the results from our association analysis if the comorbidity was resolved before the enrollment date or if the comorbidity occurred after the enrollment date. However, considering that many of the comorbidities included are chronic conditions for which diagnoses may be delayed, the potential bias might be minimal. Finally, the statistical power for the association analysis was directly linked to comorbidity prevalence, hence power may have been lacking in some comorbidities (eg, eczema/AD). Comorbidities with prevalence ≤10% overall were not analyzed for this reason and will require further attention in larger studies.

Strengths of our study are its large size, incorporating a large, heterogeneous asthma cohort from 22 countries, and generalizability of our findings to the global severe asthma population. We investigated the prevalence of 30 comorbidities, providing an in-depth analysis of prevalence patterns and permitting a comprehensive analysis of the association of individual and multiple comorbidities with multiple asthma outcomes. Future directions could include an assessment of comorbidity trajectory (ie, can biologics slow down the development of OCS-related comorbidities), the impact of the most prevalent comorbidity co-occurrences on asthma outcomes, a more detailed assessment of the clinical importance of the relationship of comorbidities and T2-related biomarkers, and the influence of comorbidities on biologic response. Addressing the relationship between comorbidities and patient behaviors (eg, adherence) would also be of interest.

In conclusion, comorbidities and multimorbidity are frequent in adults with severe asthma in real-life, and their presence is associated with poorer asthma-related outcomes. Our findings could (i) encourage a more systematic evaluation for comorbidities during routine asthma review, in line with GINA recommendations,[1] (ii) promote standardized comorbidity data collection, (iii) foster a multi-disciplinary and holistic approach to asthma management, and consequently, (iv) improve outcomes for those with severe asthma.

Acknowledgements: The authors acknowledge Mr. Joash Tan (BSc, Hons), of the Observational and Pragmatic Research Institute (OPRI), and Ms Andrea Lim (BSc, Hons) of the Observational Pragmatic Research Institute (OPRI) for their editorial and formatting assistance that supported the development of this manuscript.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2023. Published online 2023. https://ginasthma.org/wp-content/uploads/2023/05/GINA-2023-Full-Report-2023-WMS.pdf

2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Revised 2014. Published online 2014. https://ginasthma.org/wp-content/uploads/2019/01/2014-GINA.pdf

3. Patel GB, Peters AT. Comorbidities associated with severe asthma. *J Precis Respir Med*. 2019;2(1):5-9. doi:10.2500/jprm.2019.190006

4. Chanoine S, Sanchez M, Pin I, Temam S, Le Moual N, Fournier A, et al. Multimorbidity medications and poor asthma prognosis. *Eur Respir J*. 2018;51(4):1702114. doi:10.1183/13993003.02114-2017

5. Price D, Menzies-Gow A, Bachert C, Canonica GW, Kocks J, Khan AH, et al. Association Between a Type 2 Inflammatory Disease Burden Score and Outcomes Among Patients with Asthma. *J Asthma Allergy*. 2021;14:1173-1183. doi:10.2147/JAA.S321212

6. Ehteshami-Afshar S, FitzGerald JM, Carlsten C, Tavakoli H, Rousseau R, Tan WC, et al. The impact of comorbidities on productivity loss in asthma patients. *Respir Res*. 2016;17(1):106. doi:10.1186/s12931-016-0421-9

7. Chen W, Lynd LD, FitzGerald JM, Marra CA, Balshaw R, To T, et al. Excess medical costs in patients with asthma and the role of comorbidity. *Eur Respir J*. 2016;48(6):1584-1592. doi:10.1183/13993003.01141-2016

8. Chung KF. Defining phenotypes in asthma: a step towards personalized medicine. *Drugs*. 2014;74(7):719-728. doi:10.1007/s40265-014-0213-9

9. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: Clinical impact and management. *Respirology*. 2017;22(4):651-661. doi:10.1111/resp.13026

10. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193-204. doi:10.2147/JAA.S176026

11. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, 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(4):339-346. doi:10.1136/thoraxjnl-2015-207630

12. Lavoie KL, Cartier A, Labrecque M, Bacon SL, Lemière C, Malo JL, et al. Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respir Med*. 2005;99(10):1249-1257. doi:10.1016/j.rmed.2005.03.003

13. Tu X, Donovan C, Kim RY, Wark PAB, Horvat JC, Hansbro PM. Asthma-COPD overlap: current understanding and the utility of experimental models. *Eur Respir Rev*. 2021;30(159). doi:10.1183/16000617.0185-2019

14. Nadeau M, Boulay MÈ, Milot J, Lepage J, Bilodeau L, Maltais F, et al. Comparative prevalence of co-morbidities in smoking and non-smoking asthma patients with incomplete reversibility of airway obstruction, non-smoking asthma patients with complete reversibility of airway obstruction and COPD patients. *Respir Med*. 2017;125:82-88. doi:10.1016/j.rmed.2017.03.005

15. Kauppi P, Linna M, Jantunen J, Martikainen JE, Haahtela T, Pelkonen A, et al. Chronic Comorbidities Contribute to the Burden and Costs of Persistent Asthma. *Mediators Inflamm*. 2015;2015:819194. doi:10.1155/2015/819194

16. Bisaccioni C, Aun MV, Cajuela E, Kalil J, Agondi RC, Giavina-Bianchi P. Comorbidities in severe asthma: frequency of rhinitis, nasal polyposis, gastroesophageal reflux disease, vocal cord dysfunction and bronchiectasis. *Clinics (Sao Paulo)*. 2009;64(8):769-773. doi:10.1590/S1807-59322009000800010

17. Bulathsinhala L, Eleangovan N, Heaney LG, Menzies-Gow A, Gibson PG, Peters M, et al. Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study. *J Allergy Clin Immunol Pract*. 2019;7(2):578-588.e2. doi:10.1016/j.jaip.2018.08.016

18. ISAR Study Group. International Severe Asthma Registry (ISAR): Mission Statement. *Chest*. 2020;157(4):805-814.

19. International Severe Asthma Registry (ISAR). https://isaregistries.org/

20. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, et al. International severe asthma registry (ISAR): protocol for a global registry. *BMC Med Res Methodol*. 2020;20(1):212. doi:10.1186/s12874-020-01065-0

21. *Global Strategy for Asthma Management and Prevention. 2018.* Global Initiative for Asthma Management and Prevention (GINA); 2018. Accessed July 12, 2018. www.ginasthma.org

22. Cushen B, Koh MS, Tran, T. N., Martin N, Murray RB, Uthaman T. Adult severe asthma registries: a global and growing inventory. *Prag Observational Research*. Published online 2023:Submitted.

23. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. *Eur Respir J*. 1993;6 Suppl 16:5-40. doi:10.1183/09041950.005s1693

24. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. *2021*. https://www.R-project.org/

25. Wang, E., Wechsler, M. E., Tran, T. N., Heaney, L. G., Jones, R. C., Menzies-Gow, A. N., et al. Characterization of severe asthma worldwide: data from the International Severe Asthma Registry (ISAR). *Chest*. 2020;157(4):805-814.

26. Al Efraij K, Johnson KM, Wiebe D, Sadatsafavi M, FitzGerald JM. A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma. *J Asthma*. 2019;56(12):1334-1346. doi:10.1080/02770903.2018.1539100

27. Gurnell M, Heaney LG, Price D, Menzies-Gow A. Long-term corticosteroid use, adrenal insufficiency and the need for steroid-sparing treatment in adult severe asthma. *J Intern Med*. 2021;290(2):240-256. doi:10.1111/joim.13273

28. Scadding G, Walker S. Poor asthma control?--then look up the nose. The importance of co-morbid rhinitis in patients with asthma. *Prim Care Respir J*. 2012;21(2):222-228. doi:10.4104/pcrj.2012.00035

29. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir J*. 2009;18(4):300-305. doi:10.4104/pcrj.2009.00037

30. Steppuhn H, Langen U, Scheidt-Nave C, Keil T. Major comorbid conditions in asthma and association with asthma-related hospitalizations and emergency department admissions in adults: results from the German National Health Telephone Interview Survey (GEDA) 2010. *BMC Pulm Med*. 2013;13:46. doi:10.1186/1471-2466-13-46

31. Janson C, Lisspers K, Ställberg B, Johansson G, Thuresson M, Telg G, et al. Prevalence, characteristics and management of frequently exacerbating asthma patients: an observational study in Sweden (PACEHR). *Eur Respir J*. 2018;52(2). doi:10.1183/13993003.01927-2017

32. Khan AH, Gouia I, Kamat S, Johnson R, Small M, Siddall J. Prevalence and Severity Distribution of Type 2 Inflammation-Related Comorbidities Among Patients with Asthma, Chronic Rhinosinusitis with Nasal Polyps, and Atopic Dermatitis. *Lung*. 2023;201(1):57-63. doi:10.1007/s00408-023-00603-z

33. Price DB, Buhl R, Chan A, Freeman D, Gardener E, Godley C, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med*. 2018;6(1):29-39. doi:10.1016/S2213-2600(17)30424-1

34. Soremekun S, Heaney LG, Skinner D, Bulathsinhala L, Carter V, Chaudhry I, et al. Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax*. Published online August 3, 2022:thoraxjnl-2021-217032. doi:10.1136/thorax-2021-217032

35. Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *Am J Respir Crit Care Med*. 2020;201(3):276-293. doi:10.1164/rccm.201904-0903SO

36. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy*. 2016;9:1-12. doi:10.2147/JAA.S97973

37. Özden Mat D, Firat S, Aksu K, Aksu F, Duyar SŞ. Obstructive sleep apnea is a determinant of asthma control independent of smoking, reflux, and rhinitis. *Allergy Asthma Proc*. 2021;42(1):e25-e29. doi:10.2500/aap.2021.42.200098

38. Blakey J, Chung LP, McDonald VM, Ruane L, Gornall J, Barton C, 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(12):1112-1130. doi:10.1111/resp.14147

39. Suehs CM, Menzies-Gow A, Price D, Bleecker ER, Canonica GW, Gurnell M, et al. Expert Consensus on the Tapering of Oral Corticosteroids for the Treatment of Asthma. A Delphi Study. *Am J Respir Crit Care Med*. 2021;203(7):871-881. doi:10.1164/rccm.202007-2721OC

40. Liang B, Yi Q, Feng Y. Association of gastroesophageal reflux disease with asthma control. *Dis Esophagus*. 2013;26(8):794-798. doi:10.1111/j.1442-2050.2012.01399.x

41. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med*. 2017;195(3):302-313. doi:10.1164/rccm.201602-0419OC

Figure Legend.

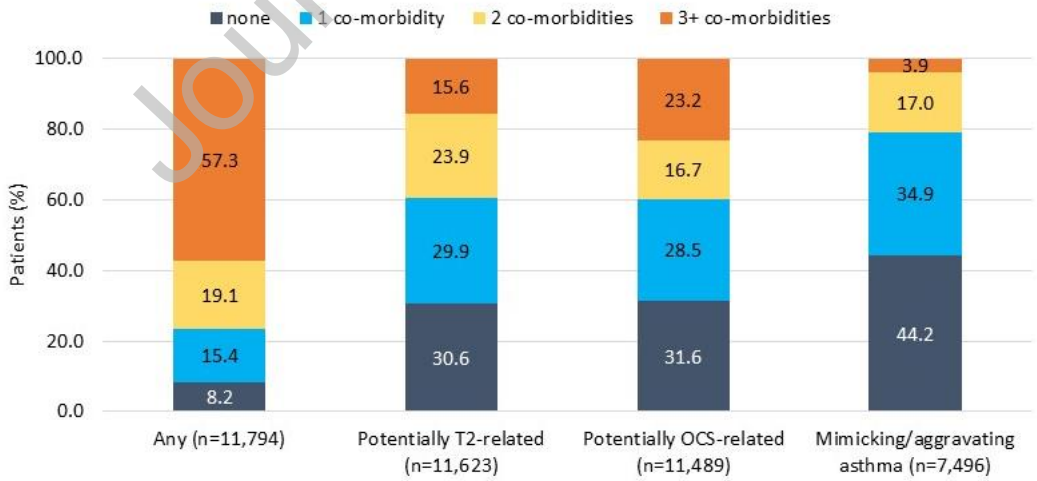


Figure 1: Proportion of patients with 1, 2, and ≥3 comorbidities overall and by comorbidity category, in patients with available data for at least three comorbidities.

Abbreviation: OCS: oral corticosteroid

Figure 2.

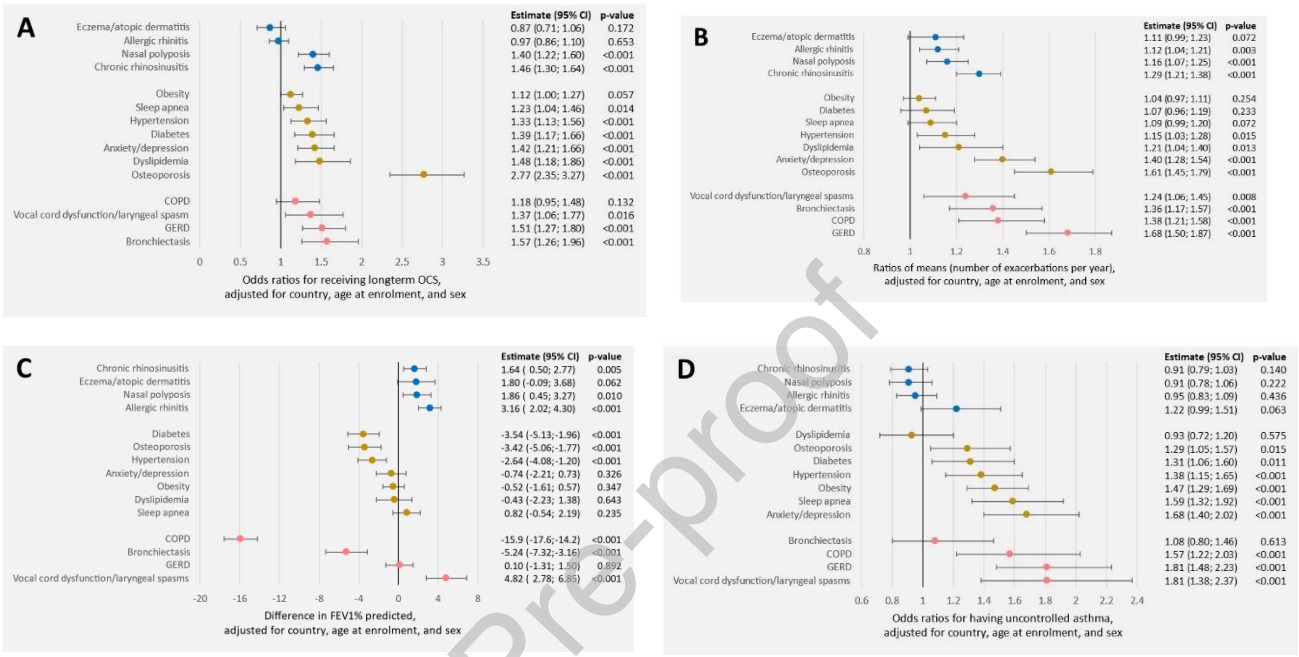


Figure 2: Association between comorbidities and (A) long-term OCS use, (B) asthma exacerbations, (C) lung function and (D) asthma control. Long-term OCS: ORs and 95% CIs of receiving long-term OCS associated with presence of comorbidities; Exacerbations: ratios of means and 95% CIs of number of exacerbations in the year preceding enrollment associated with presence of comorbidities; Percent predicted FEV_1: averaged differences and 95% CIs of FEV_1 percent predicted at enrollment associated with presence of comorbidities; (D) Asthma control: ORs and 95% CIs of having uncontrolled asthma at enrollment associated with presence of comorbidities. All associations (ORs, ratios of means and differences) were adjusted for country, age at registry enrollment and sex. Potentially T2-related comorbidities are shown in blue, potentially OCS-related

comorbidities are shown in yellow, and comorbidities mimicking/aggravating asthma are shown in pink.

Abbreviations: CI: confidence; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal reflux disease; FEV_1: forced expiratory volume in one second; OR: odds ratio. Full data, including sample sizes and p-values are available in the online supplement (**eTables 14-17**)

Table 1: Prevalence of 30 comorbid conditions in patients with severe asthma

Comorbidities	Number of contributing countries	Sample size*	N**	Prevalence
Potentially T2-related categories				
Allergic rhinitis	22	11,281	5,525	49%
Chronic rhinosinusitis[1]	21 (all -AU)	11,223	5,151	46%
Nasal polyposis	22	11,613	2,413	21%
Eczema/atopic dermatitis	22	11,600	1,199	10%
Urticaria	4 (AU, ES, UK, USA)	6,849	243	3.5%
Food allergy	5 (AU, ES, PT, UK, USA)	6,977	230	3.3%
Aspirin sensitivity	7 (AU, CA, DK, ES, PT, UK, USA)	7,498	122	1.6%
Eosinophilic esophagitis	3 (AU, UK, USA)	6,149	32	0.52%
Potentially OCS-related comorbidities				
Obesity	22	11,583	4,893	42%
Hypertension	12 (AU, ES, IT, JP, MX, PL, PT, SK, TW, UAE, UK, USA)	9,252	2,104	23%
Sleep apnea	21 (all -IT)	10,094	2,256	22%
Dyslipidemia	4 (AU, ES, UK, USA)	6,849	1,083	16%
Anxiety/depression[2]	21 (all -DK)	11,019	1,565	14%

Osteoporosis	21 (all -DK)	10,742	1,371	13%
Diabetes	22	11,422	1,336	12%
Coronary heart disease	22	11,039	984	8.9%
Pneumonia	20 (all -DK, -ES)	10,300	877	8.5%
Other significant infections	20 (all -IE, -PT)	6,918	560	8.1%
Peptic ulcer	20 (all -DK, -ES)	10,323	266	2.6%
sPulmonary embolism/VTE	20 (all -DK, -ES)	9,972	246	2.5%
Cataract	21 (all -DK)	10,923	258	2.4%
Chronic kidney disease	21 (all -DK)	11,032	164	1.5%
Adrenal insufficiency	3 (AU, UK, USA)	6,149	80	1.3%
Glaucoma	21 (all -DK)	10,888	139	1.3%
Cerebrovascular accident	20 (all -DK, -ES)	9,968	63	0.63%
	Comorbidities mimicking/aggravating asthma			
GERD[3]	7 (AU, CA, DK, ES, PT, UK, USA)	7,400	3,243	44%
COPD	7 (AU, CA, DK, ES, PT, UK, USA)	7,508	1,045	14%
Bronchiectasis	7 (AU, CA, DK, ES, PT, UK, USA)	7,509	799	11%
VCD/laryngeal spasms	5 (AU, DK, ES, UK, USA)	7,199	758	11%
Dysfunctional breathing	6 (AU, CA, DK, ES, UK, USA)	7,389	234	3.2%

1. With or without nasal polyposis
2. Can also mimic/aggravate asthma
3. Can also be OCS-related

*Variations in sample size are due to missing values for individual patients and/or at the country level.

**Number of patients with comorbidity.

Table 2: Definition and timing of collection for demographic, clinical, and asthma outcome variables

Variable	Definition/categorization	Timing of collection
Demographic characteristics		
Sex	Male/female	At enrollment
Age groups (yrs)	18-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80+	
Smoking status	Current, former, never	
Comorbidity		
Potentially T2-related	AR, CRS, NP, eczema/AD, urticaria, food allergy, aspirin sensitivity, eosinophilic esophagitis	Before or after the time of enrollment
Potentially OCS-related	Obesity, HT, SA, diabetes, dyslipidemia, anxiety/depression, OP, CHD, PN, other significant infection, peptic ulcer, PE/VTE, cataract, glaucoma, adrenal insufficiency, CVA	
Potentially mimicking/aggravating asthma symptoms	GERD, COPD, bronchiectasis, VCD/LS, dysfunctional breathing	
Clinical characteristics		
Age of asthma onset (yrs)	<12 and ≥12	At enrollment
BEC (cells/μL)	Test result	

Serum IgE (IU/mL)		Highest count prior to initiating bx or highest count ever recorded for those not receiving bx.
FeNO (ppb)		
Asthma outcomes		
LTOCS use	Yes/no and defined as daily use of OCS as a background therapy for more than 3 months	At enrollment
Exacerbation rate	Number of exacerbations requiring rescue steroids	In the 12-month period preceding enrollment
$ppFEV_1$	<80%; ≥80%	Measured as close as possible to enrollment
Asthma control	Well-, partly- or un-controlled defined by GINA 2023,[1] ACQ or ACT.	

Table 3: Association between comorbidities and asthma clinical characteristics in patients with severe asthma

	Age at asthma onset (years) Difference[1] (95% CI)	**BEC (cells/µL)** Difference[1] (95% CI)	**IgE (IU/mL)** Difference[1] (95% CI)	**FeNO (ppb)** Difference[1] (95% CI)
Potentially T2-related comorbidities				
AR	-2.95 (-3.98; -1.92)*	+29.5 (+1.2; +57.9)*	+100.3 (+50.3; +150.2)*	+5.4 (+2.1; +8.7)*
CRS	+1.70 (+0.75; +2.64)*	+158.9 (+131.8; +186.1)*	-5.6 (-53.3; +42.1)	+12.6 (+9.5; +15.7)*
NP	+1.10 (+0.12; +2.08)*	+200.9 (+166.7; +235.2)*	-20.7 (-79.7; +38.3)	+17.7 (+14.0; +21.5)*
Eczema/AD	-3.54 (-4.97; -2.11)*	+37.3 (-9.1; +83.6)	+271.2 (+191.9; +350.4)*	-1.5 (-6.7; +3.7)
Potentially OCS-related comorbidities				
Obesity	-0.66 (-1.66; +0.34)	-63.4 (-91.2; -35.5)*	-47.9 (-96.8; +1.0)*	-9.3 (-12.4; -6.2)*
Hypertension	+0.17 (-1.56; +1.90)	-41.7 (-76.7; -6.7)*	-14.7 (-82.2; 52.8)	-7.6 (-11.7; -3.5)*
Sleep apnea	-0.17 (-2.10; +1.76)	-38.9 (-73.3; -4.5)*	-67.0 (-130.8; -3.2)*	-7.2 (-11.2; -3.2)*
Dyslipidemia	-0.12 (-8.20; +7.96)	-6.0 (-47.4; +35.3)	-73.0 (-154.7; +8.6)	-7.8 (-13.3; -2.3)*

Anxiety/ depression	-0.87 (-2.39; +0.65)	-43.7 (-80.4; -7.0)	-51.4 (-118.7; +15.8)	-5.8 (-10.0; -1.5)*
Osteoporosis	-0.49 (-2.09; +1.11)	+43.2 (+1.8; +84.6)*	+36.7 (-38.0; +111.3)	-3.9 (-8.8; +0.9)
Diabetes	-1.94 (-3.63; -0.24)*	+3.23 (-36.9; +43.3)	-43.8 (-116.8; +29.3)	-6.8 (-11.8; -1.9)*
Potentially mimicking/aggravating asthma symptoms				
GERD	-2.61 (-5.40; +0.17)	-46.4 (-80.4; -12.4)*	-58.1 (-120.9; +4.7)	-7.4 (-11.6; -3.3)*
COPD	-2.15 (-7.33; +3.03)	-93.0 (-134.9; -51.1)*	+4.8 (-74.9; +84.5)	-11.7 (-17.1; -6.2)*
Bronchiectasis	-2.07 (-5.54; +1.40)	+112.3 (+65.1; +159.5)*	+114.4 (+30.8; +198.0)*	-5.5 (-11.2; +0.2)
VCD/laryngeal spasms	-0.52 (-6.34; +5.31)	-50.8 (-98.7; -3.0)*	-65.0 (-154.7; +24.7)	-1.8 (-7.5; +3.9)

See **eTables 10-13** for full data, sample sizes and p-values

*statistically significant

Estimates were derived from linear regressions using absence the considered individual comorbidity as the reference and adjusting for country, age at registry enrollment and sex.

Table 4: Association between comorbidity counts and asthma-related outcomes in patients with severe asthma with information available on ≥3 comorbidities

Comorbidity count	Long-term OCS use		Exacerbations/year		Percent predicted FEV_1		Uncontrolled asthma	
	Odds ratios (95% CI)	p	Ratios of means (95% CI)	p	Differences (95% CI)	p	Odds ratios (95% CI)	p
Overall (any category of comorbidities)								
0	Reference		Reference		Reference		Reference	
1	1.07 (0.85; 1.34)	0.587	0.98 (0.87; 1.12)	0.811	+0.84 (-1.43;+3.11)	0.469	1.08 (0.84; 1.39)	0.551
2	1.20 (0.96; 1.50)	0.116	1.09 (0.97; 1.24)	0.157	+0.72 (-1.49;+2.93)	0.524	1.27 (0.99; 1.63)	0.056
3+	1.87 (1.51; 2.31)	<0.001	1.51 (1.34; 1.70)	<0.001	+0.16 (-1.93;+2.25)	0.880	1.70 (1.35; 2.15)	<0.001
Potentially T2-related comorbidities								
0	Reference		Reference		Reference		Reference	
1	1.16 (0.99; 1.34)	0.058	1.14 (1.04; 1.24)	0.003	+3.73 (+2.40;+5.07)	<0.001	0.89 (0.76; 1.05)	0.179
2	1.31 (1.12; 1.52)	<0.001	1.26 (1.15; 1.37)	<0.001	+4.39 (+2.96;+5.82)	<0.001	0.91 (0.77; 1.08)	0.284
3+	1.44 (1.20; 1.72)	<0.001	1.39 (1.25; 1.55)	<0.001	+4.88 (+3.11;+6.64)	<0.001	1.05 (0.86; 1.29)	0.635
Potentially OCS-related comorbidities								
0	Reference		Reference		Reference		Reference	
1	1.37 (1.18; 1.59)	<0.001	1.18 (1.09; 1.29)	<0.001	-0.77 (-2.17;+0.63)	0.281	1.31 (1.11; 1.92)	0.001

2	1.69 (1.41; 2.03)	<0.001	1.28 (1.15; 1.42)	<0.001	-2.60 (-4.26;-0.94)	0.002	1.57 (1.28; 1.92)	<0.001
3+	2.50 (2.08; 3.00)	<0.001	1.62 (1.45; 1.80)	<0.001	-2.75 (-4.37;-1.14)	<0.001	2.36 (1.92; 2.90)	<0.001
Comorbidities mimicking/aggravating asthma								
0	Reference		Reference		Reference		Reference	
1	1.38 (1.14; 1.66)	<0.001	1.56 (1.39; 1.76)	<0.001	-1.97 (-3.55;-0.40)	0.014	2.06 (1.64; 2.60)	<0.001
2	1.73 (1.36; 2.20)	<0.001	1.82 (1.57; 2.11)	<0.001	-7.00 (-8.92;-5.09)	<0.001	2.40 (1.82; 3.18)	<0.001
3+	2.66 (1.85; 3.82)	<0.001	2.66 (2.12; 3.34)	<0.001	-10.48 (-13.71;-7.25)	<0.001	3.21 (2.04; 5.04)	<0.001

See Table 1 for co-morbidities included in each category.

Estimates obtained through: *logistic regressions, † negative binomial regressions, ‡ linear regressions. All models adjusted for country, age at registry enrollment and sex.

eSupplement

eAppendix 1.

Methods

Ethics, registration and compliance information for ISAR

The ISAR database has ethical approval from the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218) and is registered with the European Union Electronic Register of Post-Authorization studies (ENCEPP/DSPP/23720). The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) Code of Conduct (EMA 2014; EUPAS44024) and with all applicable local

and international laws and regulation, and registered with ENCEPP (https://www.encepp.eu/encepp/viewResource.htm?id=48848). Governance was provided by ADEPT (registration number: ADEPT1121).

Statistical analyses

Comorbidity prevalence

The total sample size was 11,821 patients. The sample size varied depending on the considered comorbidity or group of comorbidities. For each individual comorbidity, the denominator was computed as the number of patients with presence/absence information available on at least one visit. Prevalence estimates were calculated by dividing the number of patients with reported comorbidity by the corresponding denominator and expressed in percent. To compute the prevalence of having any comorbidity, overall and by categories, the denominator was the number of patients with non-missing data for at least one comorbidity (overall and by categories). As a sensitivity analysis, we calculated the prevalence in subgroups of patients with non-missing data for at least two, three, etc. up to the total number of considered comorbidities. To investigate the influence of contributing countries to the overall prevalence estimates, we conducted meta-analyses of country-specific prevalence estimates using generalized linear mixed models, in which we estimated the overall prevalence from random intercept logistic regression models (random effects model estimates) [Ref 1]. The overall prevalence calculated with no consideration of countries as calculated above were equivalent to meta-analysis pooled estimates from the fixed effects models.

Comorbidity counts and co-occurrences

In patients with non-missing data for at least three comorbidities, overall and by categories, we counted the number of reported comorbidities and calculated the prevalence of one, two, and three

or more comorbidities (overall and by categories). As a sensitivity analysis, we repeated this analysis in subgroups of patients with non-missing data for at least four, five, etc. up to the total number of considered comorbidities. In patients with non-missing data for at least one comorbidity in each category, we calculated the proportions of patients having no comorbidity, potentially T2-comorbidity only, potentially OCS comorbidity only, comorbidity mimicking/aggravating asthma only, any combination of comorbidity in two categories, and comorbidity in all three categories.

Association analysis

The total sample size was 8499 patients. All patients were prospectively enrolled, ie, from 1 May 2017 onward. The sample size varied depending on the considered comorbidity or group of comorbidities, and data availability of demographic and clinical characteristics. The prevalence of comorbidities by demographic characteristics (age, sex, and tobacco smoking at enrollment) were compared through univariate analysis. The difference in age distributions in patients with and without comorbidities was tested with Kruskal-Wallis rank sum tests. The differences in sex and tobacco smoking status distributions were tested with Pearson's Chi-squared tests.

The association between clinical characteristics/asthma-related outcomes and comorbidities were assessed through multivariable models both for individual comorbidities and the number of comorbidities. For the association of outcome and individual comorbidity, comorbidity (ever/never present) was the explanatory variable and clinical characteristics/asthma-related outcomes was the dependent variables, adjusting for country, age at enrollment and sex. For the association of outcome and the number of comorbidities, we used ordinal variables (0, 1, 2, or 3+ comorbidities), overall and within the comorbidity categories. For continuous dependent variables (age at asthma onset, biomarkers, and percent predicted FEV_1), we used linear regressions and results were expressed as differences comparing patients with to patients without the considered comorbidity. For binary dependent variables (LTOCS use [yes/no] and asthma control [uncontrolled/partly or well controlled]),

we used logistic regressions and results were expressed as odds ratios (ORs). The comorbidity/exacerbation rate association was investigated using negative binomial regressions. P-values were obtained from Wald's tests.

eTable 1. Operational definitions of comorbidity variables.

Label	Type	Values	Data source/variable computation
Potentially T2-related comorbidities			
Allergic rhinitis	Binary	Ever, Never, Missing	**Core ISAR data** OC countries[1], AU[2], IE[2], IT[2], PT[2]: categorical field (Current/Past/Never) DK[2]: binary field (Yes/No) ES[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Chronic rhinosinusitis*	Binary	Ever, Never, Missing	**Core ISAR data** OC countries[1], IE[2], IT[2], PT[2]: categorical field (Current/Past/Never) DK[2]: binary field (Yes/No) ES[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4] AU[2]: not collected unless presence of nasal polyps
Nasal polyposis	Binary	Ever, Never, Missing	**Core ISAR data** OC countries[1], AU[2], IE[2], IT[2], PT[2], UK[2]: categorical field (Current/Past/Never) DK[2]: binary field (Yes/No) ES[2]: checkbox[4] USA[3]: ICD codes plus free-text field[4]
Eczema/atopic dermatitis	Binary	Ever, Never, Missing	**Core ISAR data** OC countries[1], AU[2], IE[2], IT[2], PT[2], UK[2]: categorical field (Current/Past/Never) DK[2]: binary field (Yes/No) ES[2]: checkbox[4] USA[3]: ICD codes plus free-text field[4]
Urticaria	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** AU[2], ES[2], UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]
Food allergy	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** AU[2], PT[2], ES[2], UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]
Aspirin sensitivity	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** CA[1]: categorical field (Current/Past/Never) AU[2], ES[2]: checkbox[4] DK[2], PT[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]

Label	Type	Values	Data source/variable computation
Eosinophilic esophagitis	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** AU[2], UK[2]: free-text field[4] USA[2]: ICD codes plus free-text field[4]
Any potentially T2-related comorbidity	Binary	Ever, Never, Missing	The 8 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 8 comorbid conditions missing. The rest was coded Never.
Number of reported potentially T2-related comorbidities	Count	0 to 8	Each of the 8 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 8 comorbid conditions missing. The rest was coded Never.
Potentially OCS-related comorbidities			
Obesity	Binary	Ever, Never, Missing	**Core ISAR data** Defined as BMI ≥ 30kg.m^{-2}, calculated from patient's reported height and weight
Hypertension	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** OC countries[1]: free-text field[4] ("other cardiovascular disease") AU[2], IT[2], PT[2], UK[2]: free-text field[4] ES[2]: checkbox[4] USA[3]: ICD codes plus free-text field[4]
Sleep apnea	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], DK[2], IE[2], PT[2]: binary field (Yes/No) AU[2], ES[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Dyslipidemia	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Anxiety/depression	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], DK[2], IE[2], IT[2], PT[2]: binary fields (Yes/No) AU[2], ES[2]: checkboxes[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4] *Note: in countries with binary fields or checkboxes, anxiety and depression data were collected separately and pooled to create a single variable.*

Label	Type	Values	Data source/variable computation
Osteoporosis	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) AU[2], ES[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Diabetes	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], DK[2], IE[2], IT[2], PT[2]: binary field (Yes/No) AU[2]: checkbox[4] ES[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Coronary heart disease	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: two binary fields (Yes/No) for "heart failure" and "myocardial infarction", plus free-text field ("other CVD") AU[2]: checkbox[4] for "myocardial infarction" plus free-text field[4] DK[2]: checkbox[4] for "non-specified CVD" ES[2]: checkbox[4] for "ischemic heart disease" UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Pneumonia	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Other significant infections	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], DK[2], IE[2], IT[2], ES[2]: binary field (Yes/No) AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Peptic ulcer	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Pulmonary embolism/venous thromboembolism	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Cataract	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]

Label	Type	Values	Data source/variable computation
Chronic kidney disease	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) for "renal failure" AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Adrenal insufficiency	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Glaucoma	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) AU[2], UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Cerebrovascular accident	Binary	Ever, Never, Missing	**Additional ISAR data[6]** OC countries[1], IE[2], IT[2], PT[2]: binary field (Yes/No) for "stroke" AU[2]: checkbox[4] UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Any potentially OCS-related comorbidity	Binary	Ever, Never, Missing	The 17 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 17 comorbid conditions missing. The rest was coded Never.
Number of reported potentially OCS-related comorbidities	Count	0 to 17	Each of the 17 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 17 comorbid conditions missing. The rest was coded Never.
Comorbidities mimicking/aggravating asthma			
GERD	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** CA[1]: categorical field (Current/Past/Never) AU[2], ES[2]: checkbox[4] DK[2], PT[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
COPD	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** CA[1]: categorical field (Current/Past/Never) AU[2], ES[2]: checkbox[4] DK[2], PT[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]

Label	Type	Values	Data source/variable computation
Bronchiectasis	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** CA[1]: categorical field (Current/Past/Never) AU[2], ES[2]: checkbox[4] DK[2], PT[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
VCD/laryngeal spasms	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** AU[2], ES[2]: checkbox[4] DK[2], PT[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Dysfunctional breathing	Binary	Ever, Never, Missing	**Extra-ISAR data[5]** CA[1]: categorical field (Current/Past/Never) AU[2], ES[2]: checkbox[4] DK[2], PT[2]: binary field (Yes/No) UK[2]: free-text field[4] USA[3]: ICD codes plus free-text field[4]
Any comorbidity mimicking/ aggravating asthma	Binary	Ever, Never, Missing	The 5 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 5 comorbid conditions missing. The rest was coded Never.
Number of comorbidities mimicking/ aggravating asthma	Count	0 to 5	Each of the 5 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 5 comorbid conditions missing. The rest was coded Never.
All comorbidities			
Any comorbidity	Binary	Ever, Never, Missing	The 30 variables defined above for individual comorbid conditions. Ever was defined by any comorbidity coded Ever. Missing was assigned to patients with all 30 comorbid conditions missing. The rest was coded Never.
Number of reported comorbidities of any type	Count	0 to 30	Each of the 30 comorbid conditions listed above counts for 1 if coded Ever. Missing was assigned to patients with all 30 comorbid conditions missing. The rest was coded Never.

Label	Type	Values	Data source/variable computation

Abbreviations: AU: Australia; BMI: body mass index; CA: Canada; COPD: chronic obstructive pulmonary disease; CRS: chronic rhinosinusitis; CVD: cardiovascular disease; DK: Denmark; ES: Spain; GERD: gastroesophageal reflux disease; IE: Ireland; ISAR: International Severe Asthma Registry; IT: Italy; OC countries: countries using the OpenClinica platform to record data (see footnote 1); PT: Portugal; UK: United Kingdom; USA; United States of America; VCD: vocal cord dysfunction

1. 14 countries use the OpenClinica platform to record data in a standardized electronic case report form (eCRF): Argentina, Bulgaria, Canada, Colombia, Greece, India, Japan, Kuwait, Mexico, Poland, Saudi Arabia, South Korea, Taiwan, UAE.
2. 7 countries use own eCRF platform: Australia, Denmark, Ireland, Italy, Portugal, Spain, UK.
3. The USA provides data extracted from the electronic medical records (EMR).
4. For comorbidities which presence was assessed through a box field to be checked if present or through free-text field, absence of the comorbidity was assumed if the box was left unchecked or if no sign of the comorbid condition was present in the free-text field. No patients were coded with missing information.
5. Additional data provided by some participating countries, outside of the ISAR framework.
6. Data for most potentially OCS-related comorbidities were collected through the ISAR effectiveness/comorbidity bolt-on fields. Data for "other significant infections" was collected through the ISAR safety bolt-on fields.

* Whenever nasal polyposis was reported while chronic rhinosinusitis was not reported, chronic rhinosinusitis was forced to "Ever", except for Australia where chronic rhinosinusitis without nasal polyposis was not collected. Patients coded "Ever" for chronic rhinosinusitis then correspond to patient with this condition, with or without (or no information on) nasal polyposis. Patients coded "Never" for nasal polyposis and without information on chronic rhinosinusitis in general were left missing for chronic rhinosinusitis.

Three categories of ISAR variables are shown: core ISAR data, bolt-on ISAR data and extra ISAR data. Core ISAR data are variables that were identified using an ISAR-led Delphi study [Ref 2]. All countries participating in ISAR collect core ISAR variables, except Australia which collects data on nasal polyposis specifically but not on chronic rhinosinusitis in general. 'Effectiveness' bolt-on variables were OCS-related comorbidities. 'Safety' bolt-on variables assessed the safety of biologics: serious infection, anaphylaxis, and cancer. Not all countries in ISAR collect the bolt-on variables. Extra ISAR data are variables that do not fall within core or bolt-on ISAR variables, but that countries may collect as per their research interests.

eTable 2. Demographic and clinical variables used to assess for assocation with comorbidities

Label	Type	Values	Data source/variable computation
Demographic variables			
Country	Nominal	AR, AU, BG, CA, CO, DK, ES, GR, IN, IE, IT, JP, KW, MX, PT, SA, SK, TW, UAE, UK, USA	-
Age at enrollment	Numerical	≥18 years old	Completed years of age at the time of enrollment in the registry. The date of enrollment was defined as follows: - For patients who initiated biologics on or after 1 May 2017: date of biologic initiation; - For patients who did not initiate biologics: first visit occurring from 1 May 2017 onward.
Sex	Binary	Women, Men, Missing	As assessed by physician.
Smoking status at enrollment	Ordinal	Current smoker, Ex-smoker, Never smoker, Missing	As assessed by physician.
Clinical variables			
General characteristics			
Age at asthma onset	Numerical	≥0, Missing	As reported by patient. 0 means that asthma started before 1 year of age
Received biologics	Binary	Yes, No	At enrollment.
Asthma biomarkers			
Highest BEC (cells/µL)	Numerical	20 to 5000	- In patients receiving biologics: highest count recorded prior to initiating biologics - In patients not receiving biologics: highest count ever recorded
FeNO test result (parts per billion [ppb])	Numerical	1 to 300	- In patients receiving biologics: highest count recorded prior to initiating biologics - In patients not receiving biologics: highest count ever recorded

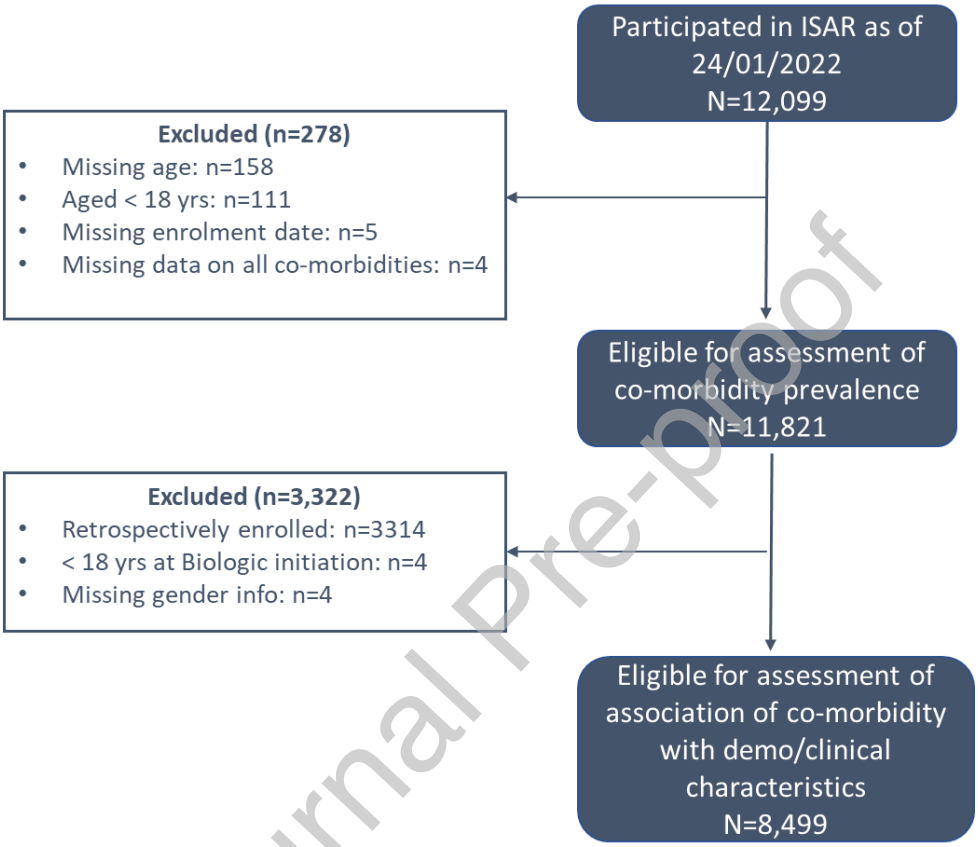
Count of blood IgE (IU/mL)	Numerical	0 to 15,600	- In patients receiving biologics: highest count recorded prior to initiating biologics - In patients not receiving biologics: highest count ever recorded
Eosinophilic phenotype ISAR algorithm[2]	Ordinal	Grade 0 to 3	Grade 0: Unlikely/non eosinophilic Grade 1: Least likely Grade 2: Likely Grade 3: Most likely
Asthma-related outcomes			
Exacerbation rate at enrollment (count per year)	Count	0 to 24	Number of exacerbations requiring rescue steroids in the 12 months preceding enrollment.
post-BD FEV_1 % predicted at enrollment	Numerical	14 to 185%	Measurement closest to enrollment.
FEV_1 /FVC	Numerical	0.20 to 1.00	Measurement closest to enrollment.
Asthma control assessment	Ordinal	Well controlled, Party controlled, Uncontrolled	As assessed closest to enrollment. Categories defined by GINA 2020 update. For countries providing ACQ or ACT instead of GINA categories, conversions were performed as follows: - ACQ: Mean ACQ ≤0.75 → Well controlled 0.75< Mean ACQ <1.5 → Partly controlled Mean ACQ ≥1.5 → Uncontrolled - ACT: Total ACT >19 → Well controlled 15< Total ACT ≤19 → Partly controlled Total ACT ≤15 → Uncontrolled
Long-term OCS use at enrollment	Binary	Yes, No, Missing	-
Long-term OCS daily dose at enrollment	Numerical	0.5 to 100 mg	-

Abbreviations: ACQ: Asthma control questionnaire; ACT: Asthma control test; AR: Argentina; AU: Australia; BEC: blood eosinophil count; BG: Bulgaria; CA: Canada; CO: Colombia; ES: Spain; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; IN: India; ISAR: International Severe Asthma Registry; IT: Italy; IU: International unit; JP: Japan; KW: Kuwait; MX: Mexico; OCS: Oral corticosteroids; PB: post-bronchodilator; PT: Portugal; SA: Saudi Arabia; SK: South Korea; TW: Taiwan; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America

Results

Subject disposition

eFigure 1: Subject disposition



ISAR: International Severe Asthma Registry

Baseline characteristics

Patients in both assessment cohorts, were predominantly female (62%), aged 50-69 years at enrollment (50%), had later onset asthma (ie, aged ≥12 yrs; ~80%) and an eosinophilic phenotype (~87%). 23% of patients were receiving LTOCS at enrollment (**eTable 3A & 3B**).

Patients included in the cohort used to assess the association between comorbidity and demographic/clinical characteristics tended to have poor lung function (% predicted FEV_1 <80%: 59.6%, n=3751/6292) and uncontrolled asthma (54.7%; n=2752/5031). Overall, 28.5% (2113/7422) of these patients experienced ≥2 exacerbations in the year preceding enrollment, 48.6% (n=3014/6199) had evidence of irreversible air flow obstruction and 38.2% (n=3246/8499) were on biologic therapy **(eTable 3B).**

eTable 3A: Baseline characteristics for patients included in the comorbidity prevalence assessment

Characteristics	All eligible patients (N=11,821)		Patients with non-missing data for ≥1 comorbidity in all three categories (N=7,561)		p-values[1]
	N	%	N	%	
Sex					
Denominator	11,811		7560		
Women	7352	62.2	4596	60.8	0.012[2]
Men	4459	37.8	2964	39.2	
Age at registry enrollment (years)					
Denominator	11,821		7561		
18-29	942	7.97	622	8.23	
30-39	1162	9.83	705	9.32	
40-49	1893	16.0	1141	15.1	
50-59	2997	25.4	1826	24.2	
60-69	2867	24.3	1914	25.3	
70-79	1617	13.7	1115	14.7	
80+	343	2.90	238	3.15	
Median [Q1; Q3]	56 [45; 66]		57 [45; 67]		0.111[3]
Range	18 to 95		18 to 95		
Age at asthma onset (years)					
Denominator	5778		1889		
<12	1194	20.7	573	30.3	<0.001[2]
≥12	4584	79.3	1316	69.7	
Median [Q1; Q3]	30 [15; 45]		25 [8; 41]		
Range	1 to 84		1 to 78		
Receiving long-term oral corticosteroids at enrollment					
Denominator	11,745		7552		
Yes	2792	23.7	1877	24.9	0.019[2]
No	8953	76.2	5675	75.2	
Initiated biologics at enrollment					
Denominator	11,821		7561		
Yes	5428	45.9	3096	40.9	<0.001[2]
No	6393	54.1	4465	59.1	
Positive test for allergens (SPT or serum test)					
Denominator	7393		4357		
Yes	5057	68.4	3173	72.8	<0.001[2]
No	2336	31.6	1184	27.2	
Eosinophilic gradient [Ref 3]					
Denominator	7261		4504		
Grade 0: Unlikely/noneosinophilic	32	0.441	13	0.29	
Grade 1: Least likely	319	4.39	116	2.56	
Grade 2: Likely	591	8.14	279	6.19	
Grade 3: Most likely	6319	87.0	4096	90.9	<0.001[4]
Calendar year at enrollment					
Denominator	11,821		7561		
2010	3	0.03	3	0.04	
2011	0	0	0	0	
2012	4	0.03	0	0	
2013	5	0.04	2	0.03	
2014	8	0.07	2	0.03	
2015	523	4.42	515	6.81	

2016	615	5.20	608	8.04	
2017	4189	35.4	3862	51.1	
2018	2021	17.1	1410	18.6	
2019	1947	16.5	685	9.06	
2020	1602	13.6	333	4.40	
2021	892	7.55	140	1.85	
2022	12	0.102	1	0.01	<0.001[5]
Denominator	11,821		7561		
Median [Q1; Q3]	0.71 [0; 2.11]		1.08 [0; 3.00]		<0.001[3]
Range	0 to 4.52		0 to 4.27		
Country					
Denominator	11,821		7561		
Argentina	103	0.871	0	0	<0.001[6]
Australia	405	3.43	405	5.36	<0.001[6]
Bulgaria	343	2.90	0	0	<0.001[6]
Canada	274	2.32	263	3.48	<0.001[6]
Colombia	301	2.55	0	0	<0.001[6]
Denmark	350	2.96	328	4.34	<0.001[6]
Greece	142	1.20	0	0)	<0.001[6]
India	178	1.51	0	0	<0.001[6]
Ireland	20	0.17	0	0	<0.001[6]
Italy	1538	13.0	0	0	<0.001[6]
Japan	197	1.67	0	0	<0.001[6]
Kuwait	297	2.51	0	0	<0.001[6]
Mexico	144	1.22	0	0	<0.001[6]
Poland	72	0.61	0	0	<0.001[6]
Portugal	128	1.08	121	1.60	<0.001[6]
Saudi Arabia	208	1.76	0	0	<0.001[6]
South Korea	163	1.38	0	0	<0.001[6]
Spain	700	5.92	700	9.26	<0.001[6]
Taiwan	285	2.41	0	0	<0.001[6]
UAE	229	1.94	0	0	<0.001[6]
UK	712	6.02	712	9.42	<0.001[6]
USA	5032	45.6	5032	66.6	<0.001[6]

Abbreviations: Q1: quartile 1; Q3: quartile 3; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America

[1]Comparisons of the subgroup to the whole study population

[2]One-sample chi-squared proportions tests with continuity correction (to compare the distributions of binary variables)

[3]One-smaple Wilcoxon signed-rank test with continuity correct (to compare medians)

[4]One-sample chi-squared proportions tests with continuity correct comparing the proportions of patients with Grade 4

[5]One-sample chi-squared proportions tests with continuity correction comparing the proportions of patients enrolled from 2017 on

[6]One-sample chi-squared proportions tests with continuity correction comparing the proportions for each country

eTable 3B: Baseline characteristics for patients included in the association between comorbidities and demographic/clinical characteristics assessment (n=8,499)

Characteristics	N	(%)
Total	8499	
Sex		
Denominator	*8499*	
Women	5306	(62.4)
Men	3193	(37.6)
Age at registry enrollment (years)		
Denominator	*8499*	
18-29	632	(7.44)
30-39	827	(9.73)
40-49	1325	(15.6)
50-59	2138	(25.2)
60-69	2076	(24.4)
70-79	1234	(14.5)
80+	267	(3.14)
Median [Q1; Q3]	56 [45; 66]	
Range	18 to 95	
Calendar year at enrollment		
Denominator	*8499*	
2017	3196	(37.6)
2018	1803	(21.2)
2019	1533	(18.0)
2020	1290	(15.2)
2021	669	(7.87)
2022	8	(0.0941)
Duration of follow-up since enrollment (years)		
Denominator	*8499*	
Median [Q1; Q3]	1.00 [0; 2.46]	
Range	0 to 4.64	
Country		
Denominator	*8499*	
Argentina	94	(1.11)
Australia	258	(3.04)
Bulgaria	319	(3.75)
Canada	200	(2.35)
Colombia	258	(3.04)
Denmark	206	(2.42)
Greece	99	(1.16)
India	174	(2.05)
Ireland	20	(0.235)
Italy	1287	(15.1)
Japan	179	(2.11)
Kuwait	152	(1.79)
Mexico	78	(0.918)

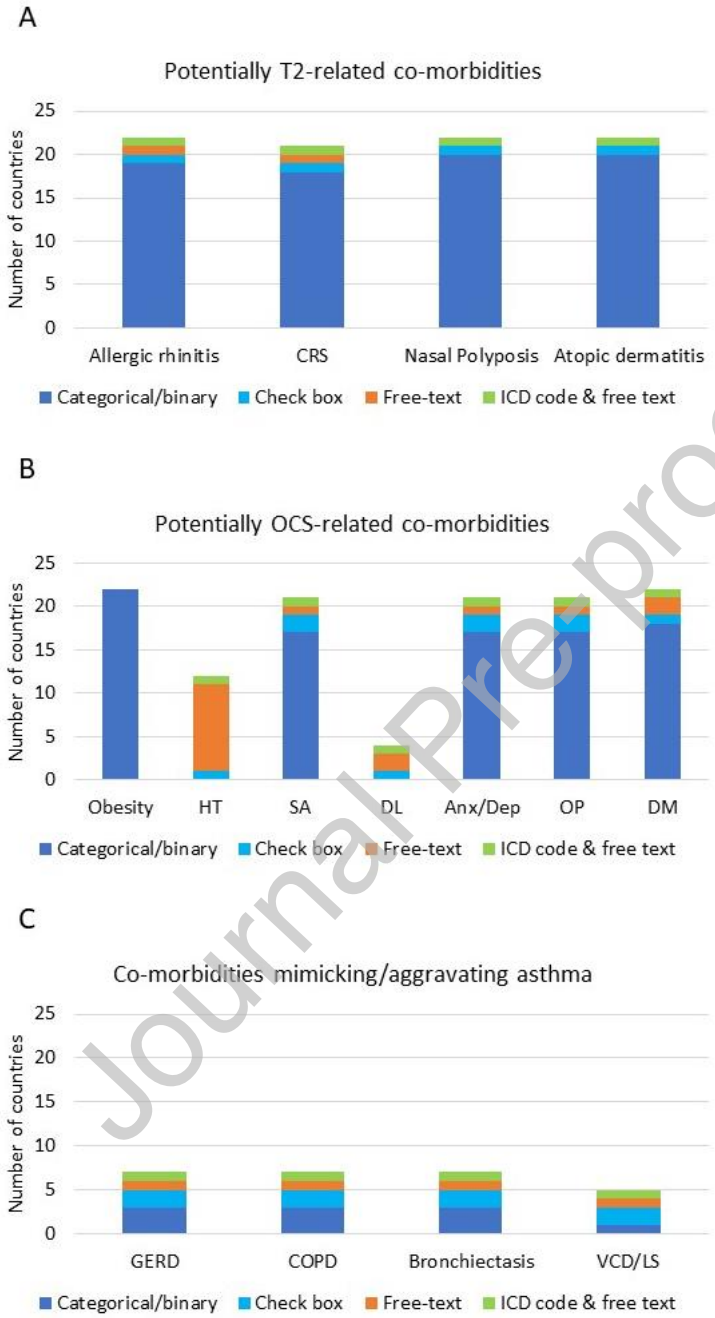
Poland	59	(0.694)
Portugal	98	(1.15)
Saudi Arabia	184	(2.16)
South Korea	158	(1.86)
Spain	445	(5.24)
Taiwan	271	(3.19)
The United Arab Emirates (UAE)	191	(2.25)
The United Kingdom (UK)	569	(6.69)
The United States of America (USA)	3200	(37.7)
Smoking status at enrollment		
Denominator	*6859*	
Current smoker	386	(5.63)
Ex-smoker	2067	(30.1)
Never smoker	4406	(64.2)
Age at asthma onset (years)		
Denominator	*4574*	
<12	874	(19.1)
≥12	3700	(80.9)
Median [Q1; Q3]	32 [17; 46]	
Range	1 to 84	
Receiving long-term OCS at enrollment		
Denominator	*8423*	
Yes	1932	(22.9)
No	6491	(77.1)
Initiated biologics at enrollment		
Denominator	*8499*	
Yes	3246	(38.2)
No	5253	(61.8)
Exacerbation rate at enrollment (number of episodes in the year preceding enrollment)		
Denominator	*7422*	
0	3751	(50.6)
1	1553	(20.9)
2	826	(11.1)
3-6	1003	(13.5)
7-12	250	(3.37)
13-24	34	(0.458)
Median [Q1; Q3]	0 [0; 2]	
Range	0 to 24	
FEV_1 percent of predicted at enrollment		
Denominator	*6292*	
<80%	3751	(59.6)
≥80%	2541	(40.4)
Median [Q1; Q3]	75.2% [60.5%; 88.9%]	
Range	14% to 185%	
Ratio of FEV_1/FVC at enrollment		
Denominator	*6199*	

<0.70	3014	(48.6)
≥0.70	3185	(51.4)
Median [Q1; Q3]	0.70 [0.61; 0.78]	
Range	0.20 to 1.00	
Asthma control assessment at enrollment (GINA 2020)		
Denominator	*5031*	
Uncontrolled	2752	(54.7)
Partly controlled	1294	(25.7)
Well controlled	985	(19.6)
Highest blood eosinophil count (cells/µL)		
Denominator	*5819*	
Median [Q1; Q3]	400 [200; 650]	
Range	20 to 5000	
Highest blood IgE count (IU/mL)		
Denominator	*4896*	
Median [Q1; Q3]	136 [42.4; 392]	
Range	0 to 12,200	
Highest FeNO test result (ppb)		
Denominator	*3581*	
Median [Q1; Q3]	30 [16; 59]	
Range	1 to 300	
Positive test for allergens (SPT or serum test)		
Denominator	5305	
Yes	3432	(64.7)
No	1873	(35.3)
Eosinophilic gradient [Ref 3]		
Denominator	*5751*	
Grade 0: Unlikely/non eosinophilic	28	(0.487)
Grade 1: Least likely	286	(4.97)
Grade 2: Likely	466	(8.10)
Grade 3: Most likely	4971	(86.4)

Abbreviations: FeNO: fractional exhaled nitric oxide; FEV_1: post-bronchodilator forced expiratory volume in 1 second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; IgE: immunoglobulin E; IU: international unit; ppb: parts per billion; OCS: oral corticosteroids; Q3: 1st quartile; Q3: 3rd quartile.

Method of comorbidity data collection

eFigure 2: Data collection methods used to capture comorbidity information in ISAR

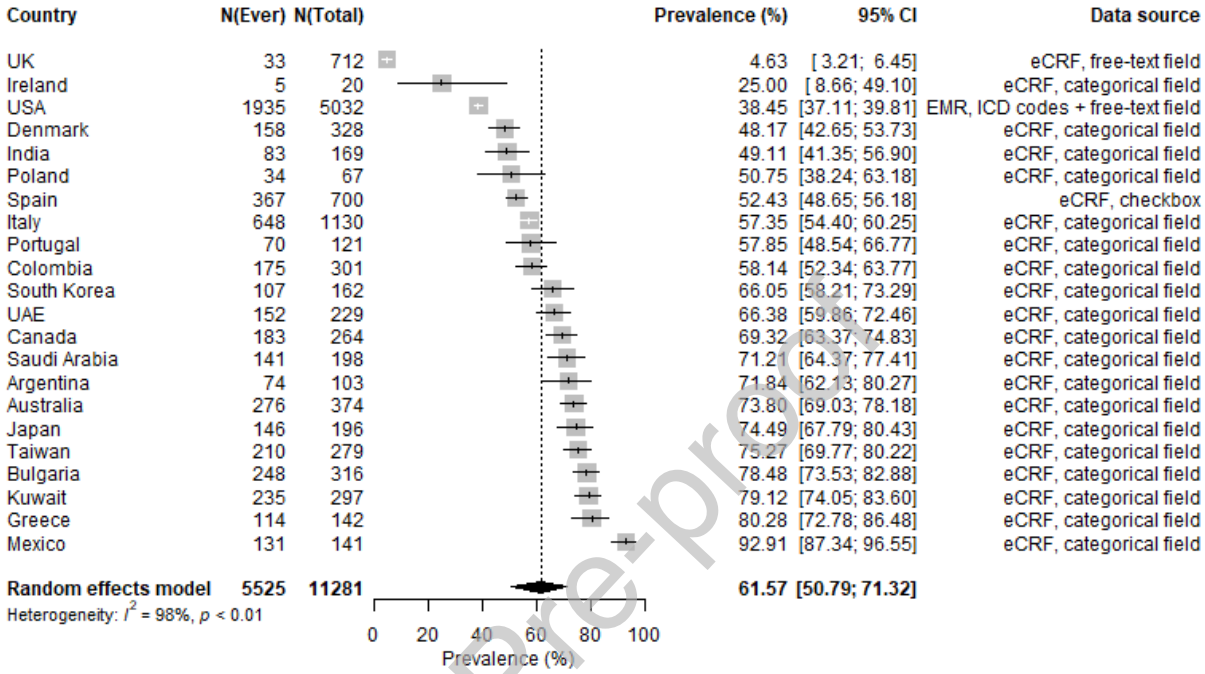


Abbreviations: Anx/Dep: anxiety/depression; COPD: chronic obstructive pulmonary disease; CRS: chronic rhinosinusitis; DL: dyslipidemia; DM: diabetes mellitus; GERD: gastroesophageal reflux disease; HT: hypertension; OCS: oral corticosteroid; OP: osteoporosis; SA: sleep apnea; VCD/LS: vocal cord dysfunction/laryngeal spasm

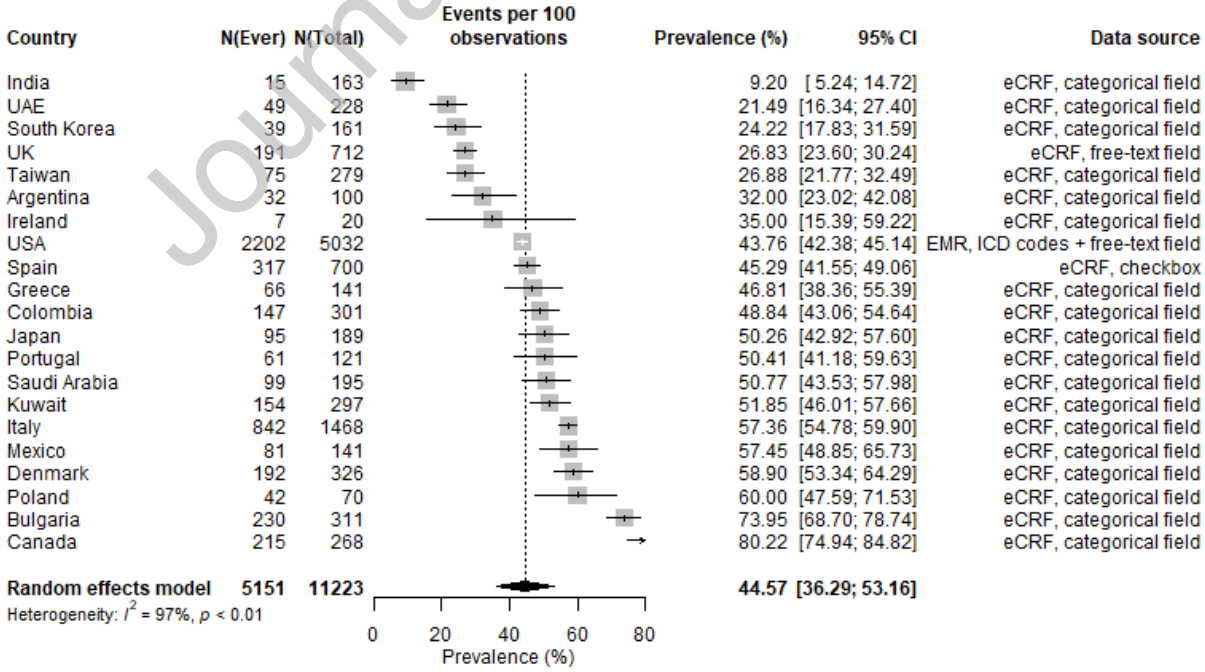
Comorbidity prevalence by countries

eFigure 3: Prevalence estimates for each recorded comorbidity by country

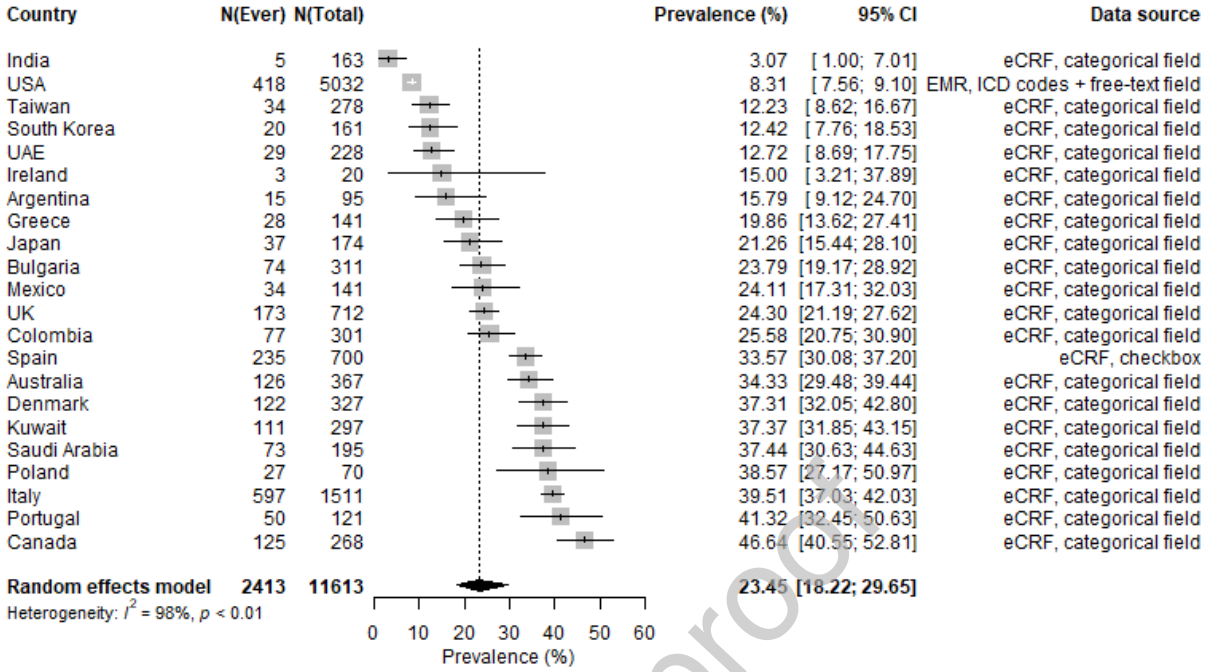
1) Allergic rhinitis



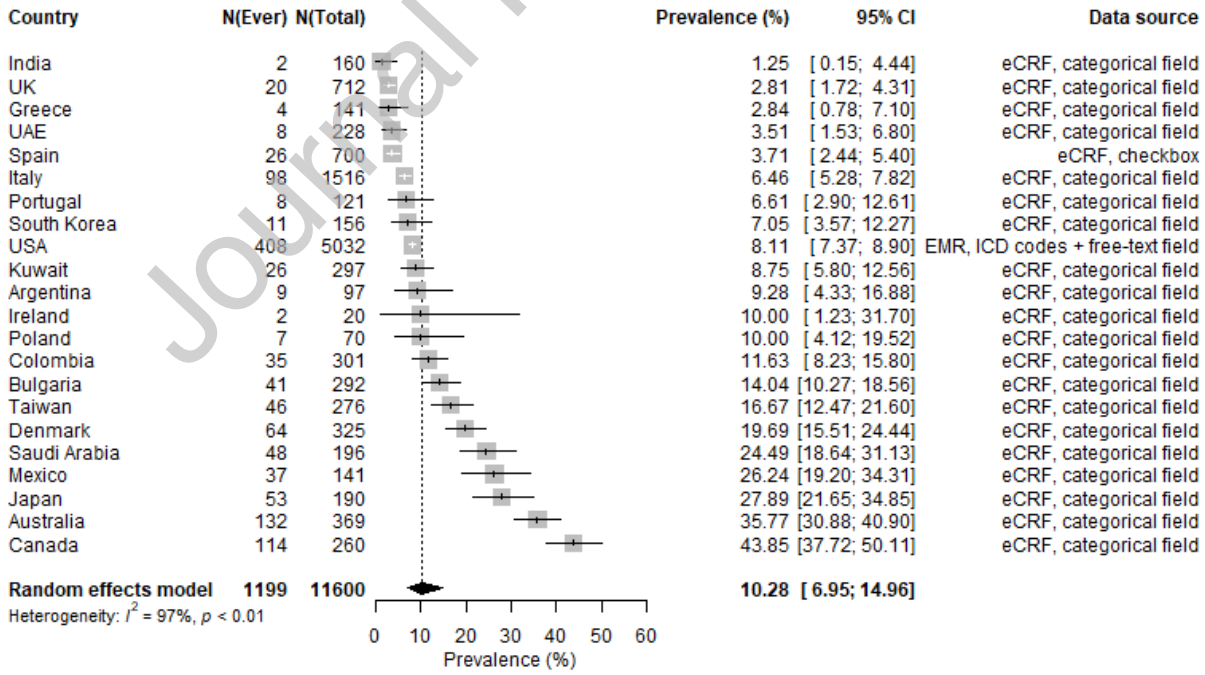
2) Chronic rhinosinusitis



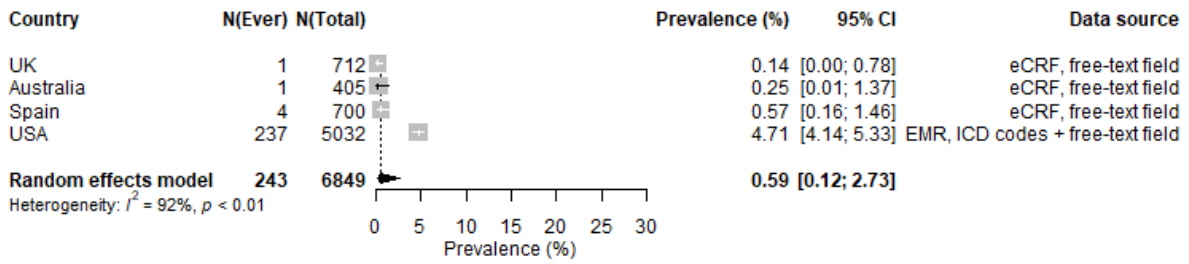
3) Nasal polyposis



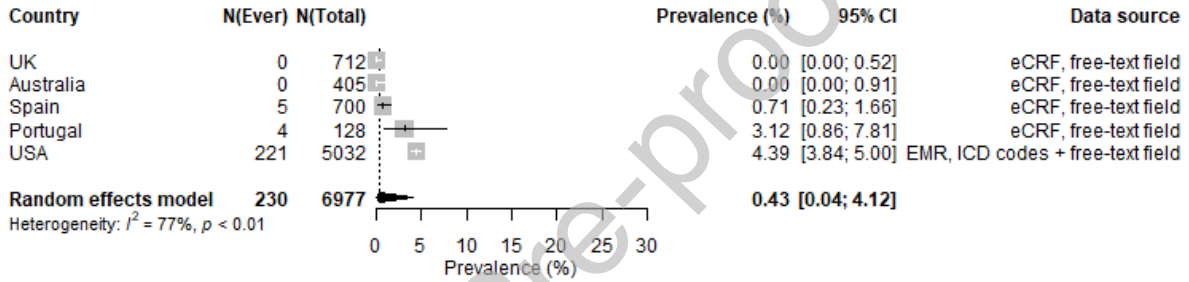
4) Eczema/atopic dermatitis



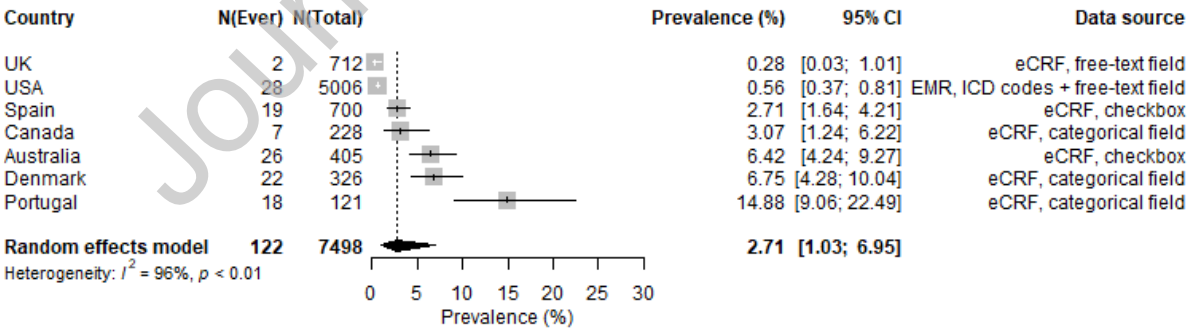
5) Urticaria



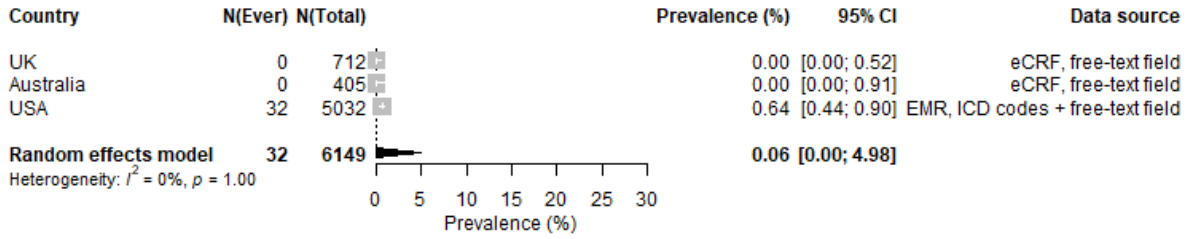
6) Food allergy



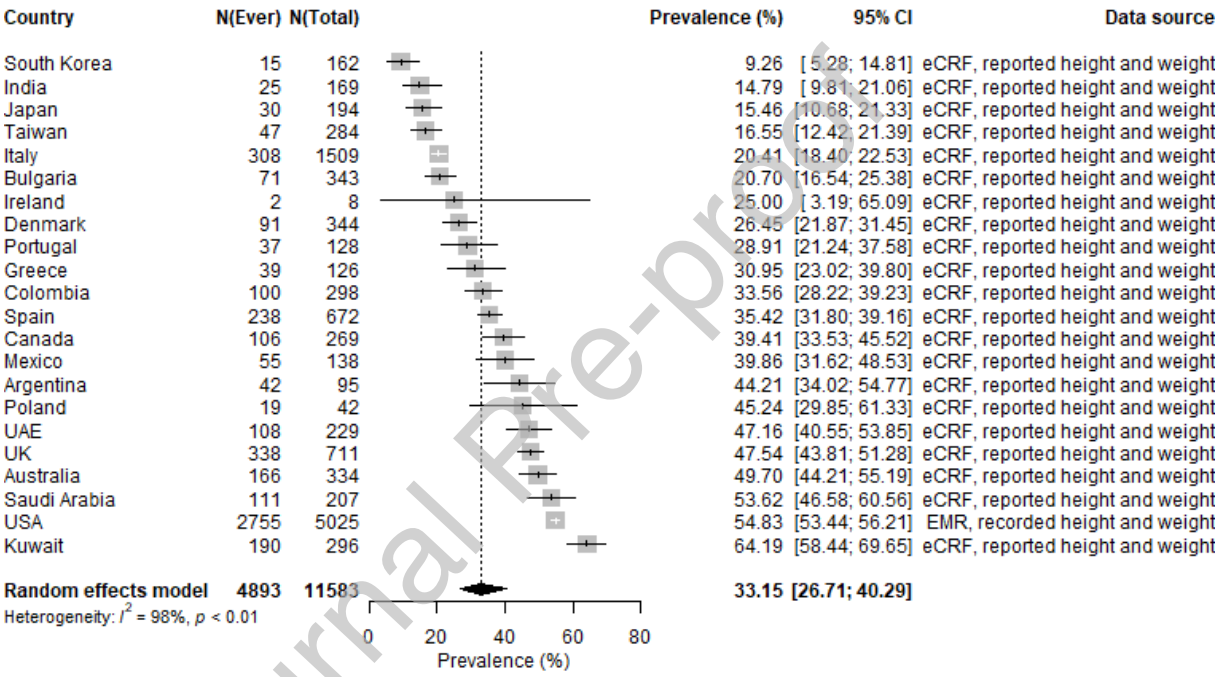
7) Aspirin sensitivity



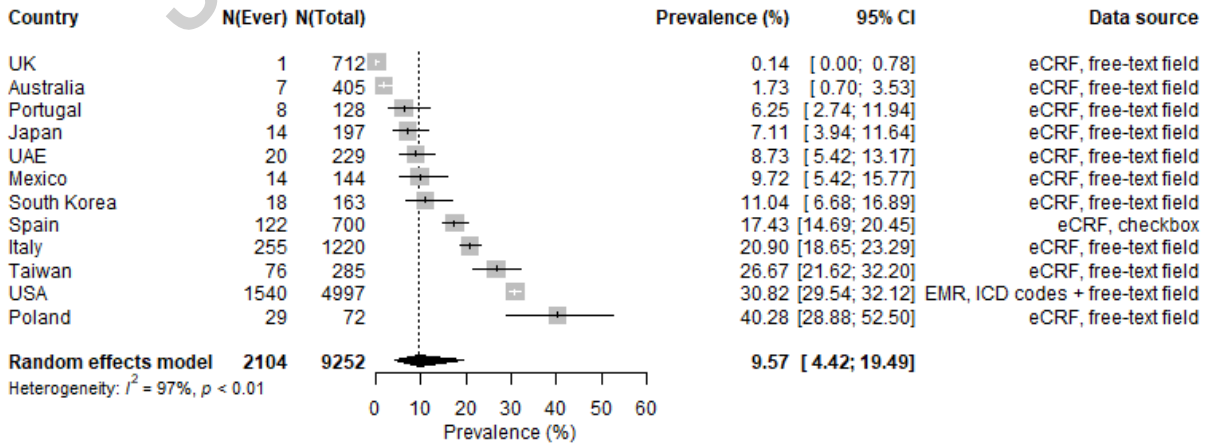
8) Eosinophilic esophagitis



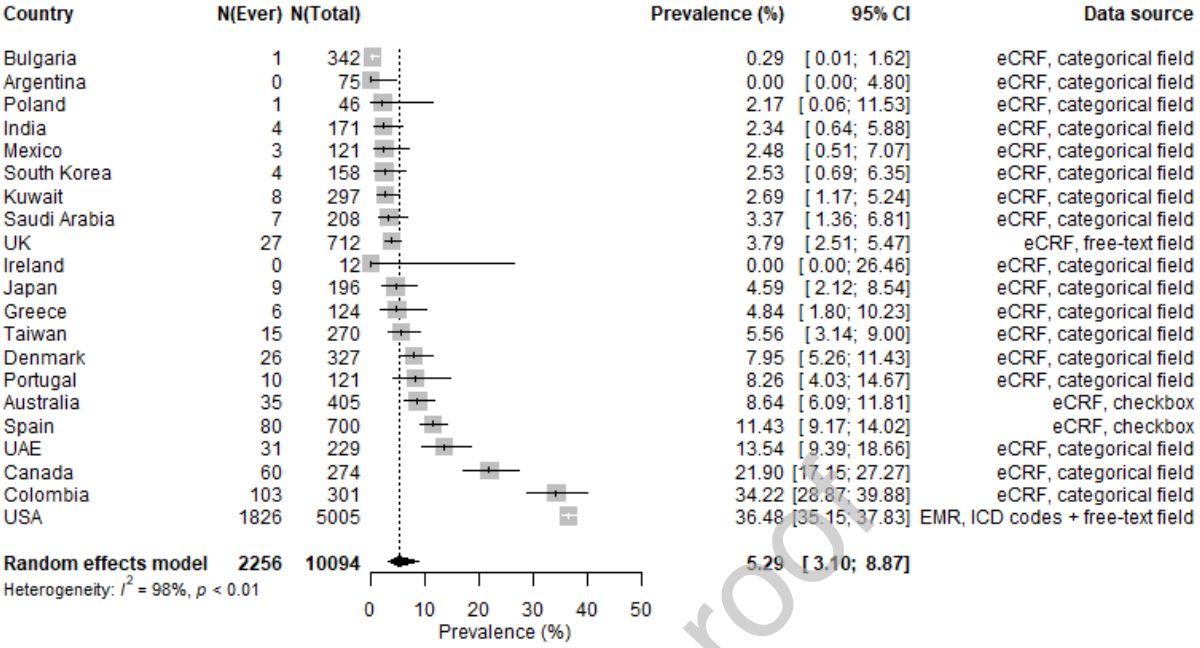
9) Obesity



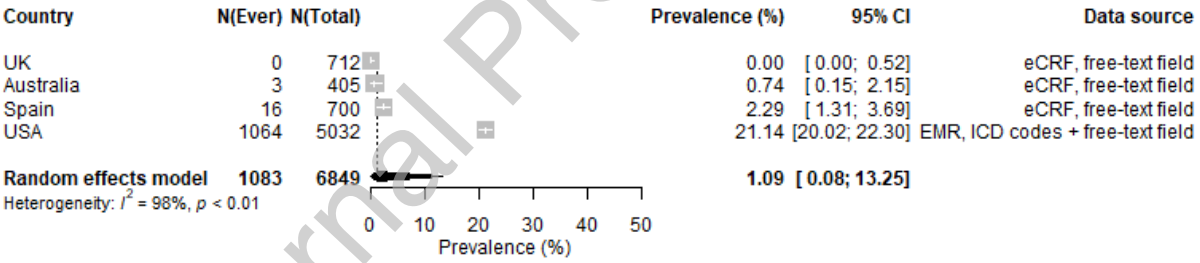
10) Hypertension



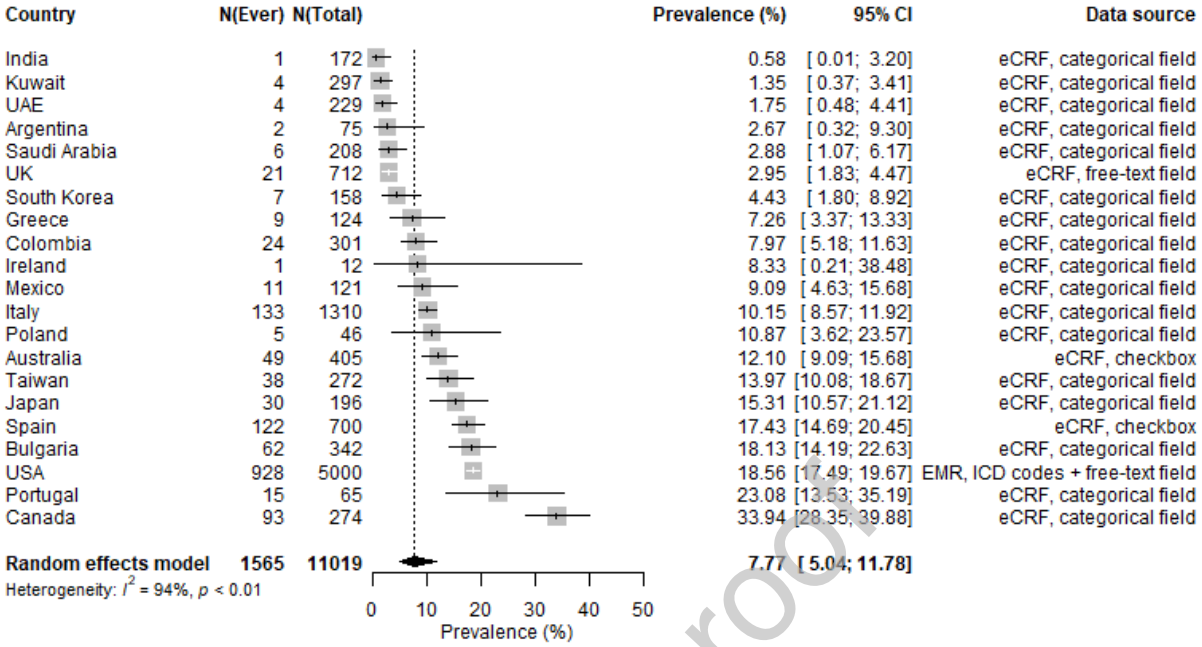
11) Sleep apnea



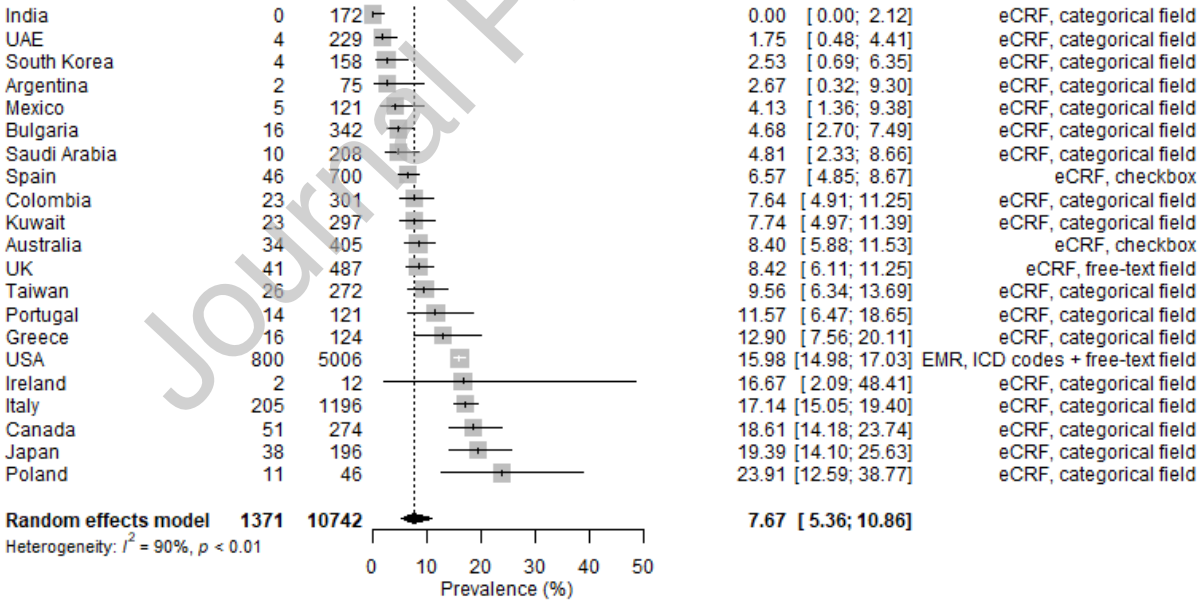
12) Dyslipidemia



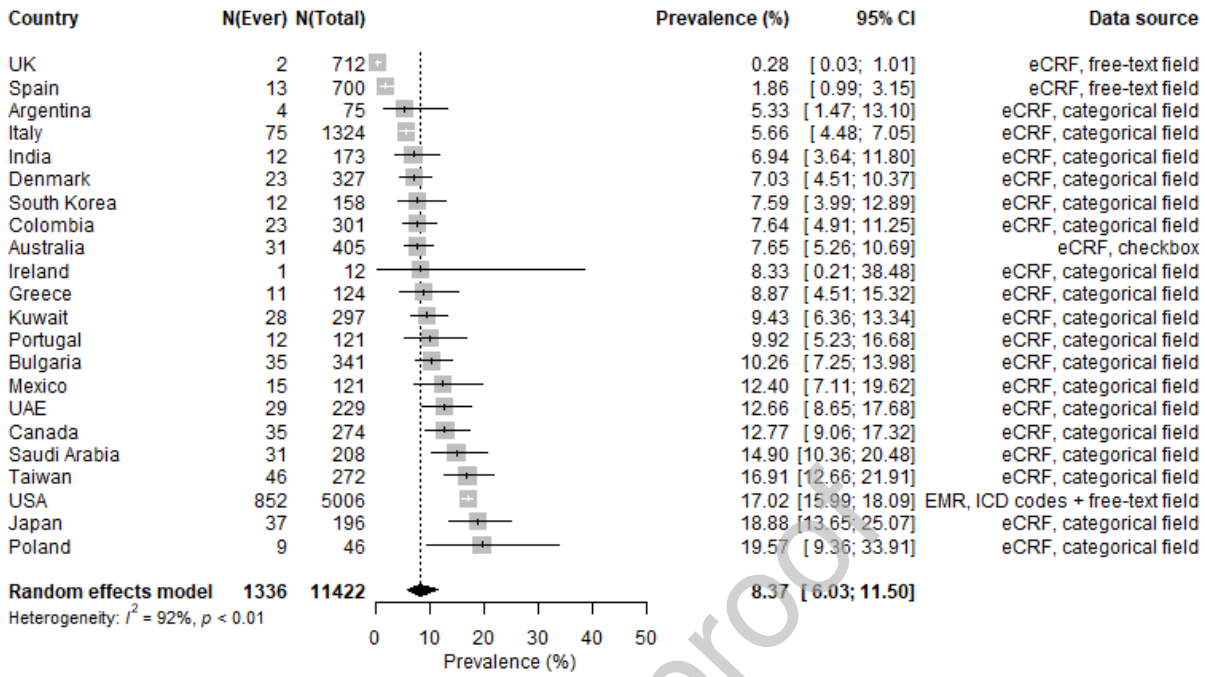
13) Anxiety/depression



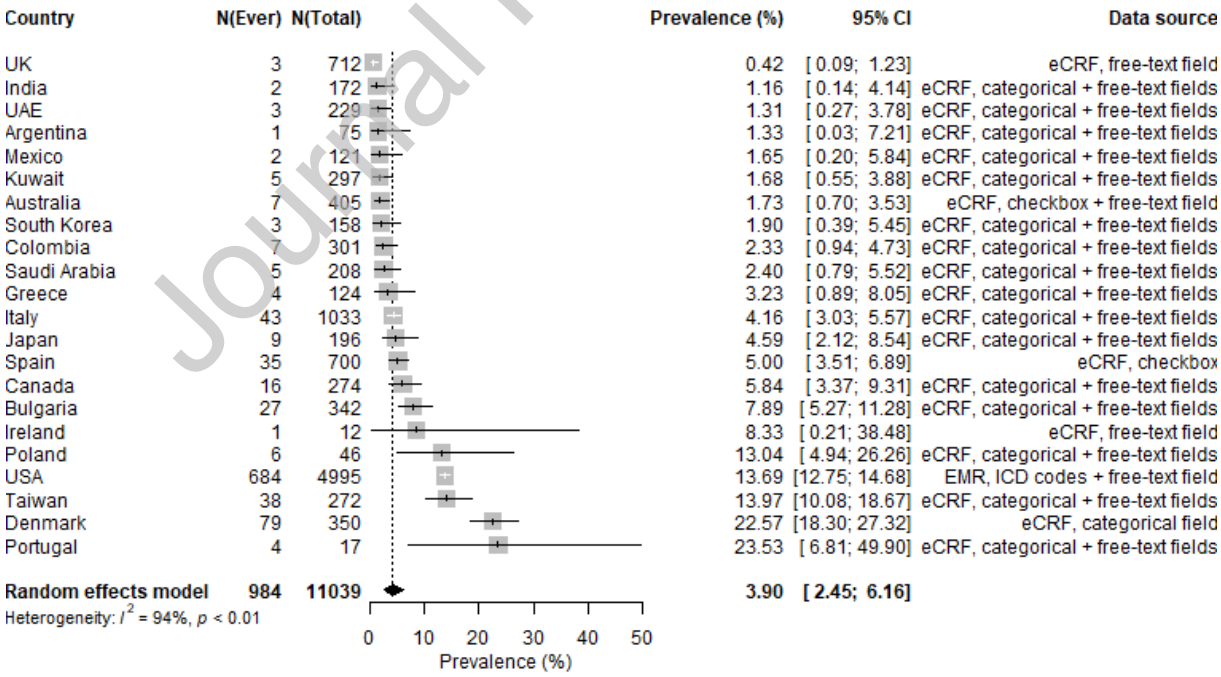
14) Osteoporosis



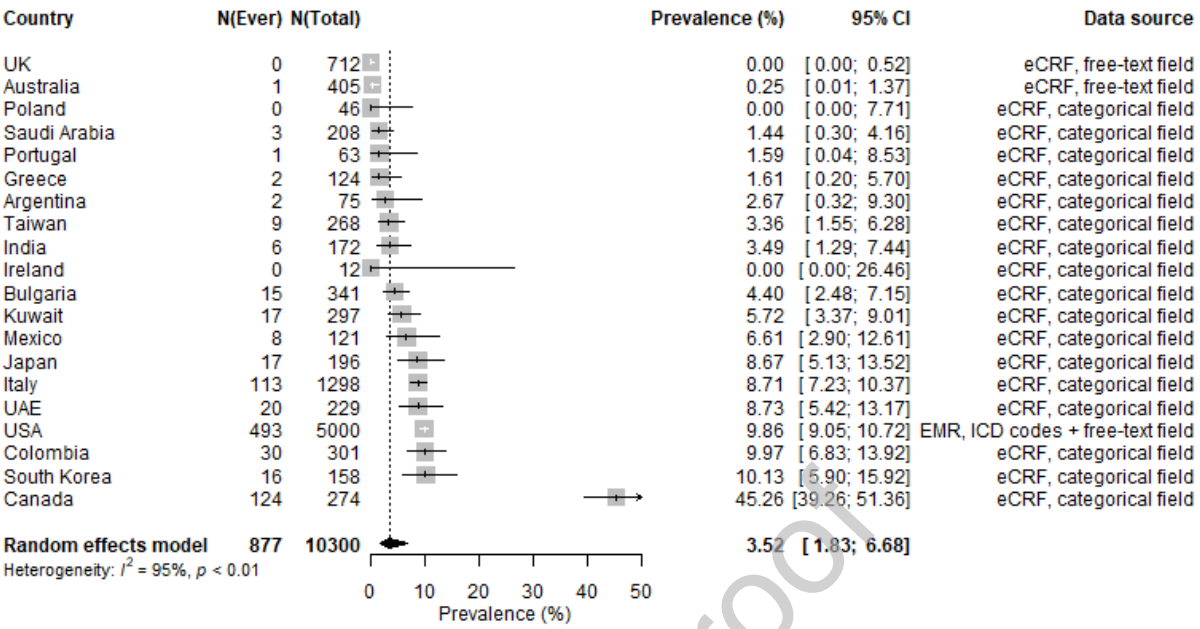
15) Diabetes



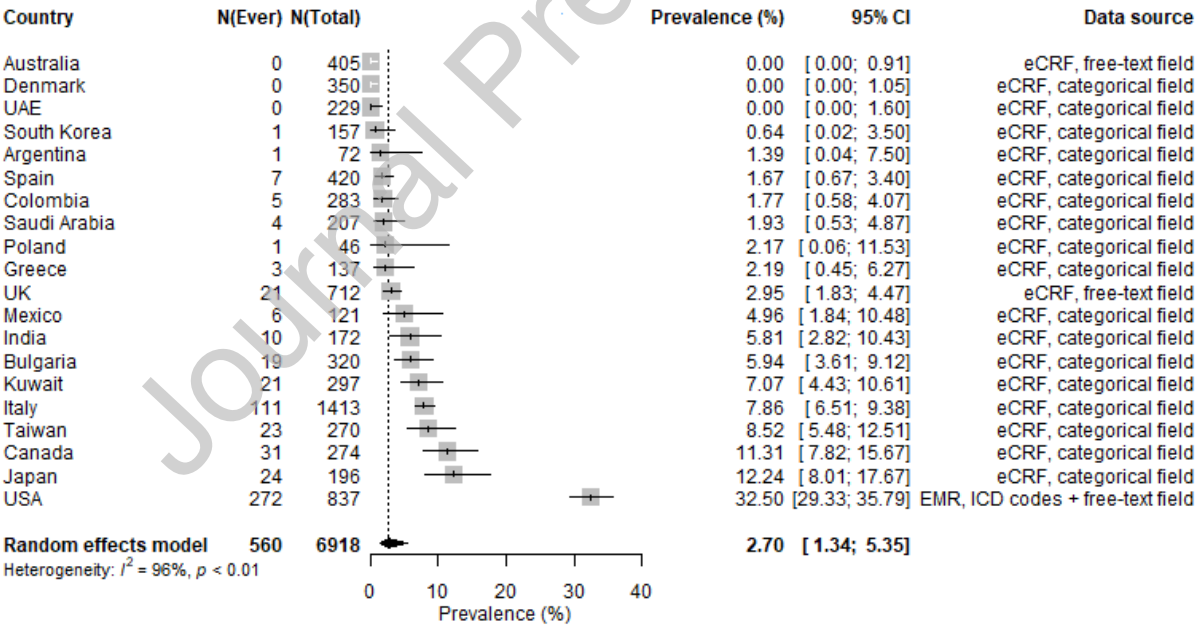
16) Coronary heart disease



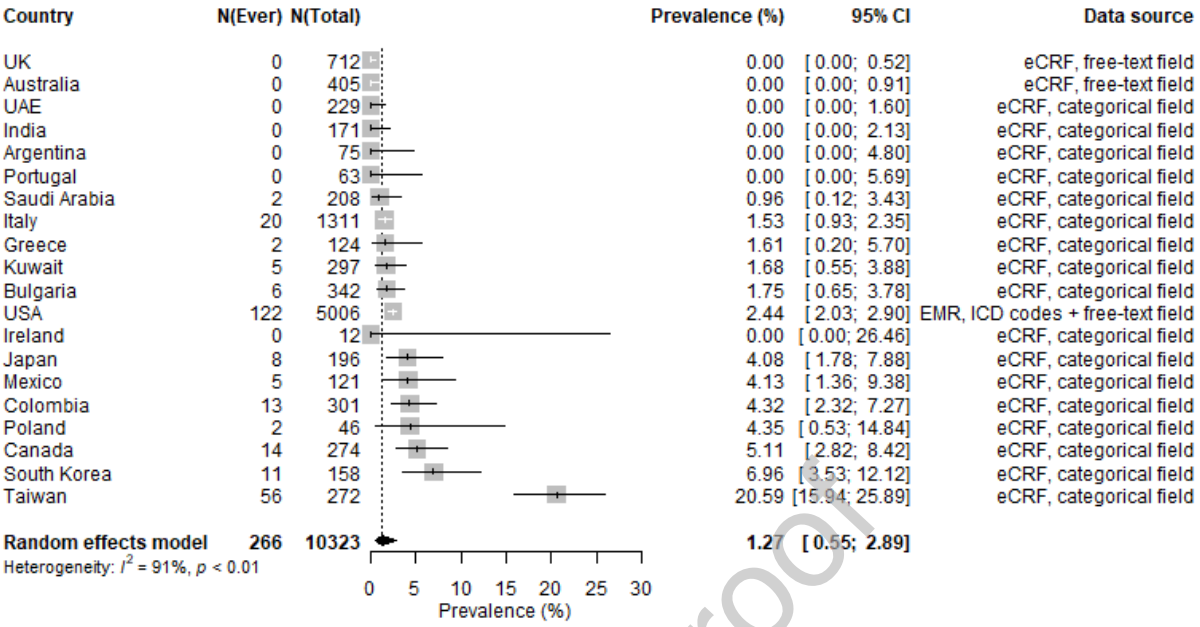
17) Pneumonia



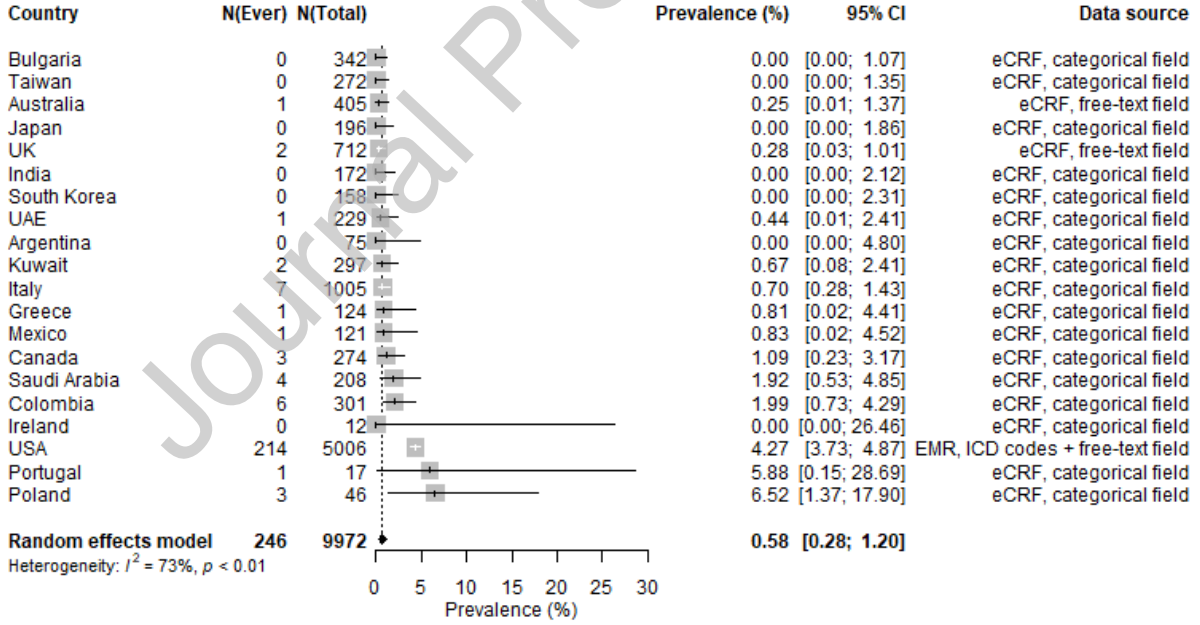
18) Other significant infections



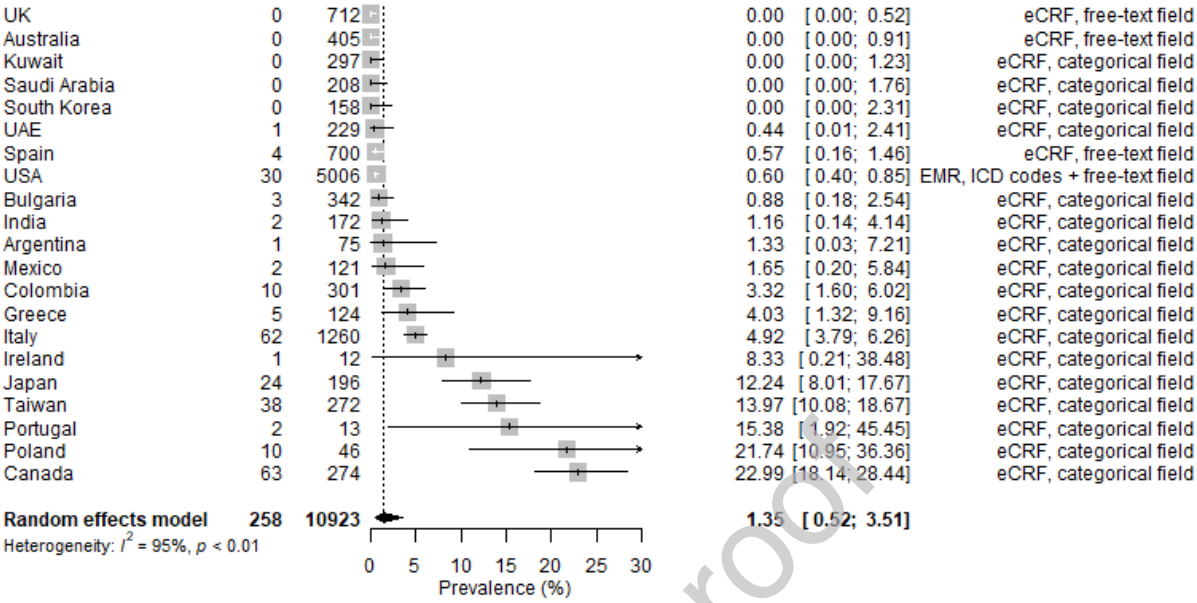
19) Peptic ulcer



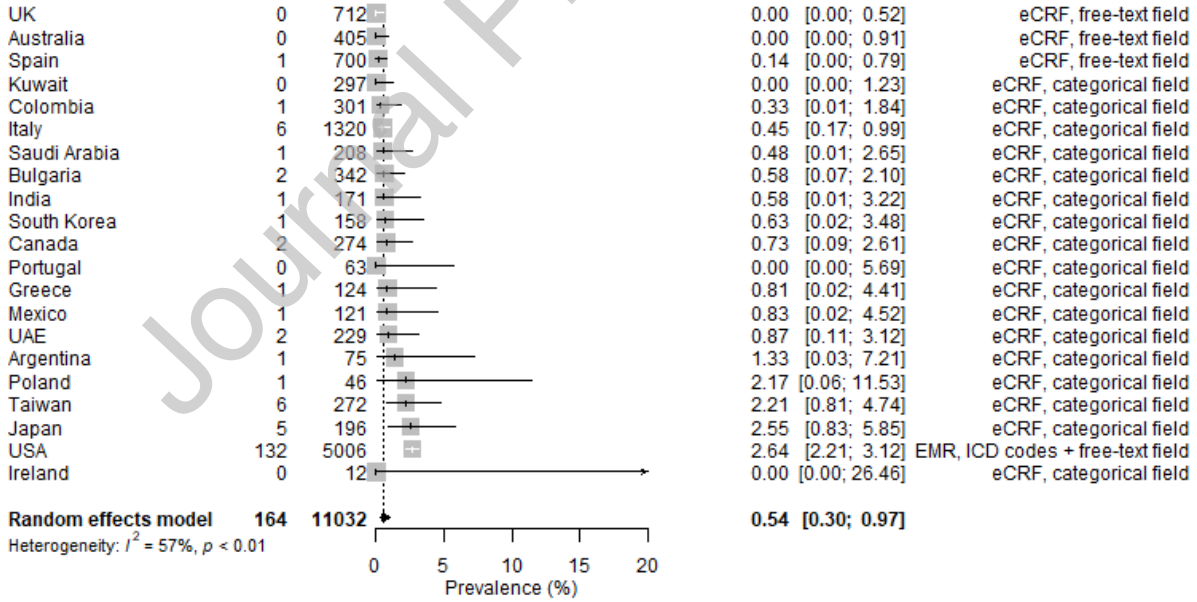
20) Pulmonary embolism/venous thromboembolism



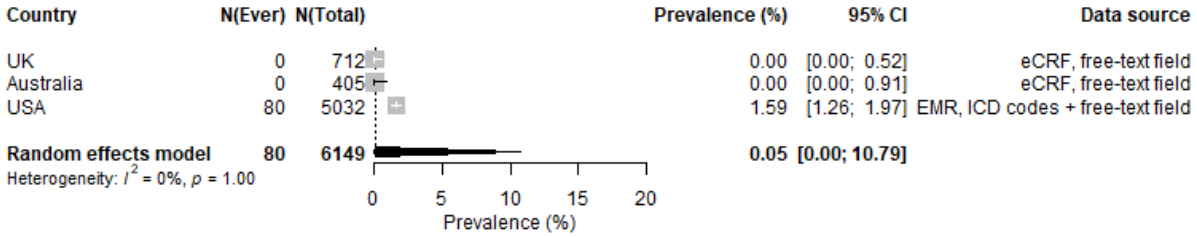
21) Cataract



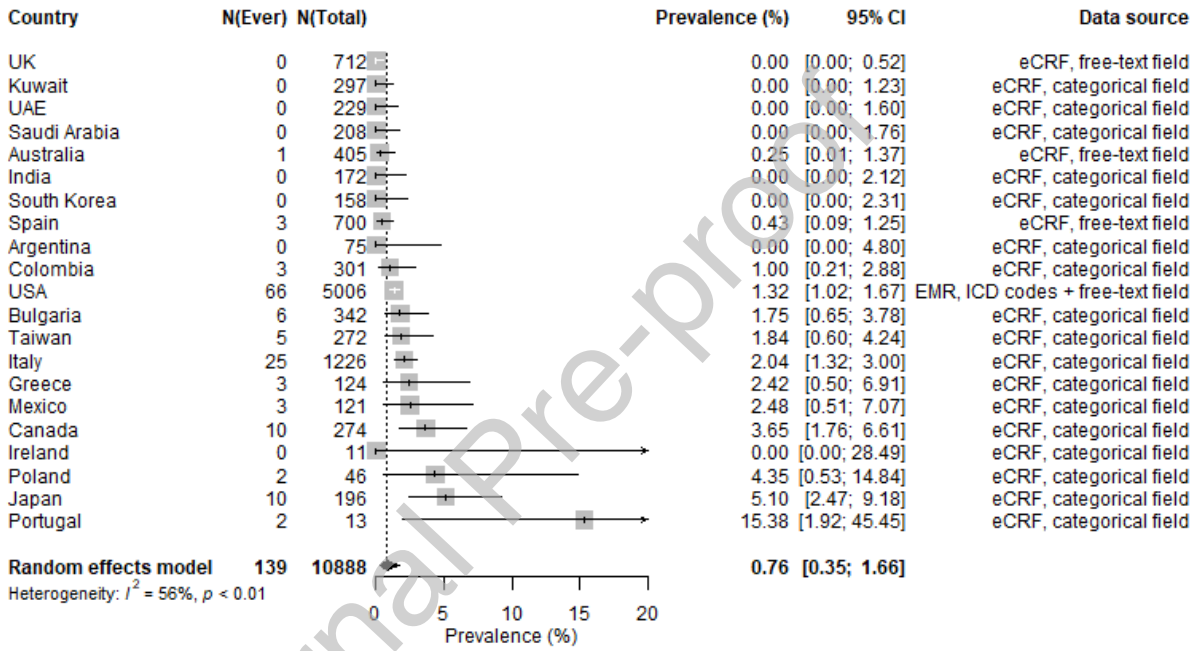
22) Chronic kidney disease



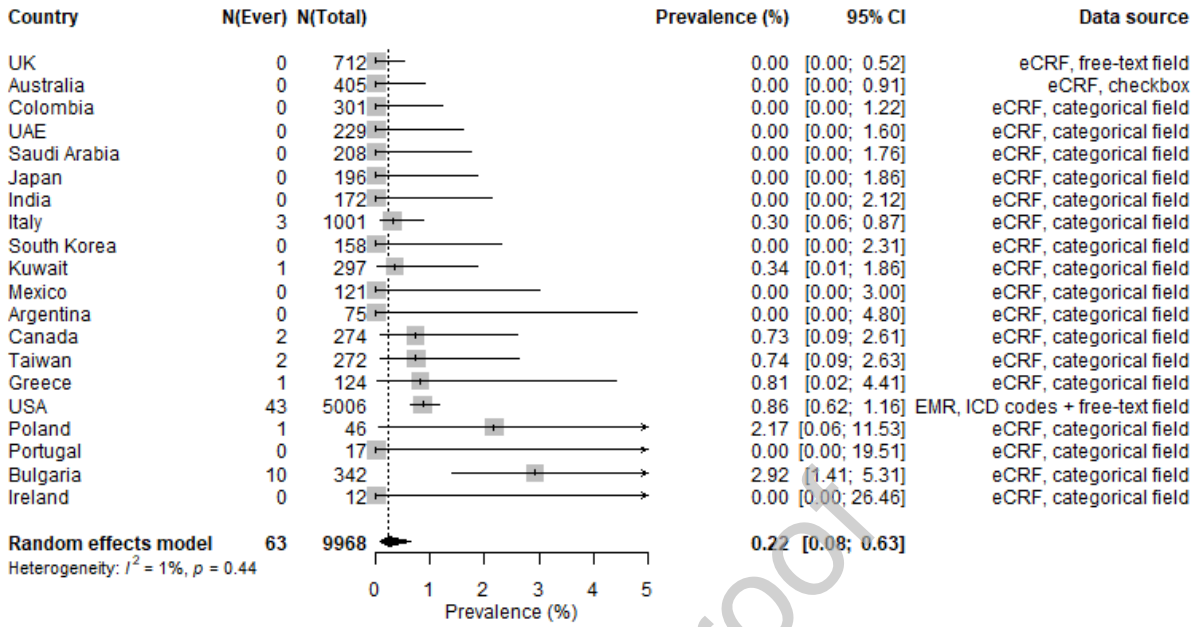
23) Adrenal insufficiency



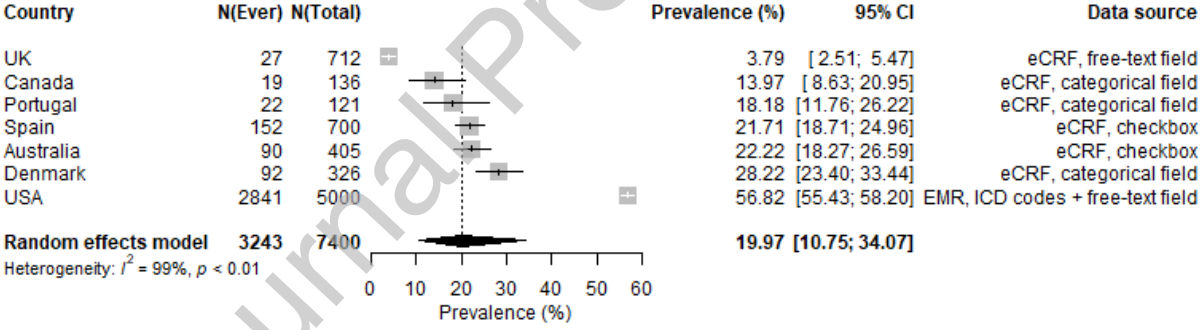
24) Glaucoma



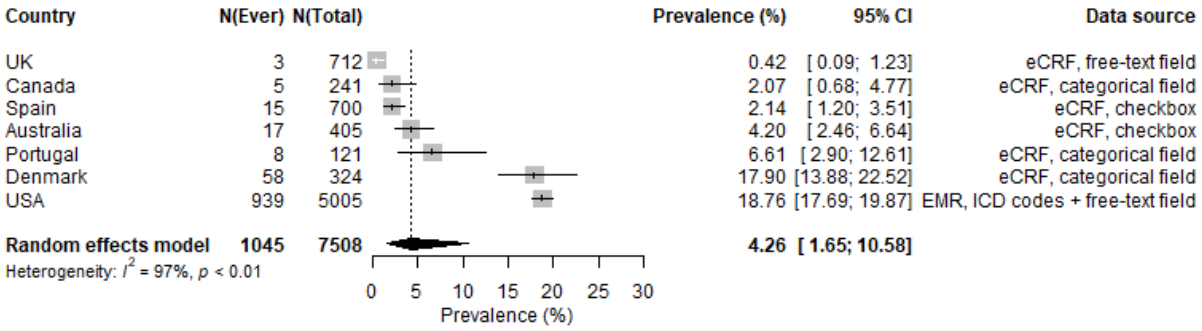
25) Cerebrovascular accident



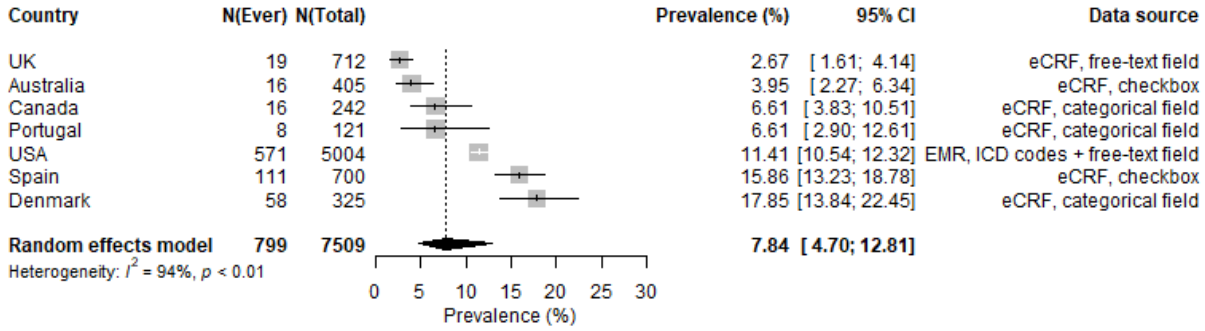
26) Gastroesophageal reflux disease



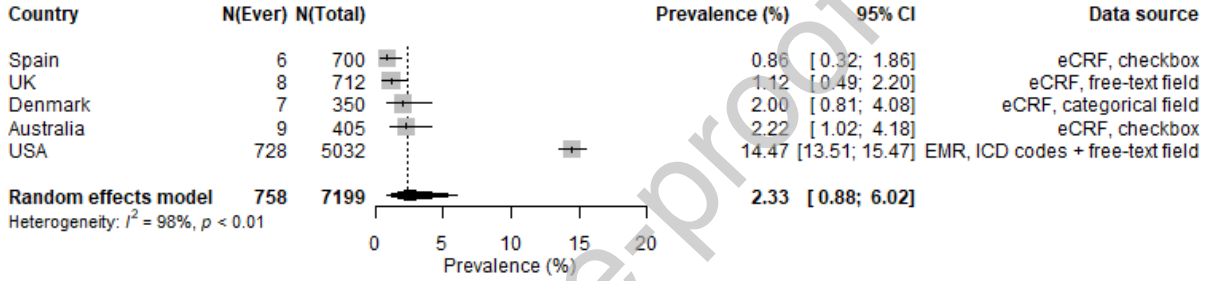
27) Chronic obstructive pulmonary disease



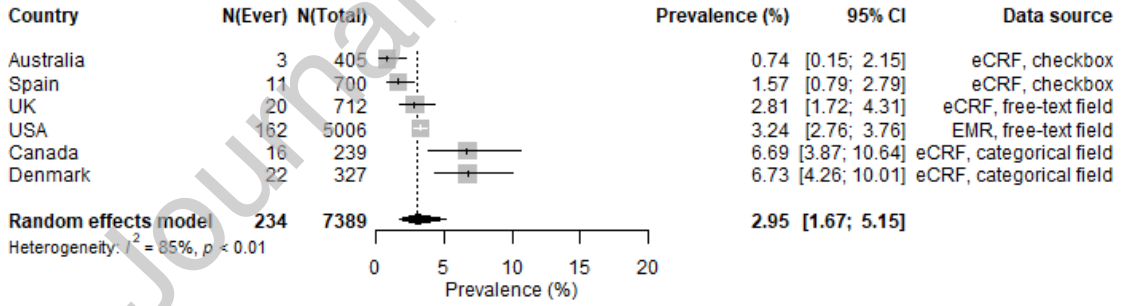
28) Bronchiectasis



29) Vocal cord dysfunction/laryngeal spasms



30) Dysfunctional breathing



Prevalence of having at least one comorbidity

eTable 4 Prevalence of having at least one comorbidity, overall and by categories, by minimum number of comorbidities with available presence/absence information.

Min number of comorbidities with presence/absence info by categories	Number of contributing countries	Sample size	N	Prevalence of having at least one comorbidity
Comorbidities of any type				
≥1	22	11,821	10,837	92%
≥2	22	11,811	10,834	92%
≥3	22	11,794	10,826	92%
≥4	22	11,744	10,810	92%
≥5	22	11,683	10,773	92%
≥6	22	11,556	10,677	92%
≥7	22	11,468	10,596	92%
≥8	22	11,461	10,589	92%
≥9	22	11,454	10,582	92%
≥10	22	11,446	10,574	92%
≥11	22	11,438	10,566	92%
≥12	22	11,405	10,534	92%
≥13	22	11,386	10,515	92%
≥14	22	11,317	10,449	92%
≥15	22	11,119	10,265	92%
≥16	21 (all -DK)	10,623	9,801	92%
≥17	21 (all -DK)	10,510	9,701	92%
≥18	20 (all -DK, -IE)	10,173	9,399	92%
≥19	12 (AU, CA, ES, JP, MX, PL, PT, SK, TW, UAE, UK, USA)	8,060	7,519	93%
≥20	6 (AU, CA, ES, PT, UK, USA)	7,096	6,649	94%
≥21	6 (AU, CA, ES, PT, UK, USA)	7,088	6,641	94%
≥22	6 (AU, CA, ES, PT, UK, USA)	7,035	6,588	94%
≥23	6 (AU, CA, ES, PT, UK, USA)	6,909	6,462	94%
≥24	4 (AU, ES, UK, USA)	6,529	6,109	94%
≥25	3 (AU, UK, USA)	6,122	5,723	93%
≥26	3 (AU, UK, USA)	6,119	5,723	94%
≥27	3 (AU, UK, USA)	6,089	5,703	94%
≥28	3 (AU, UK, USA)	6,077	5,693	94%
≥29	3 (AU, UK, USA)	5,987	5,614	94%
30	2 (UK, USA)	1,322	1,190	90%
Potentially T2-related categories				
≥1	22	11,743	8,120	69%
≥2	22	11,697	8,100	69%
≥3	22	11,623	8,071	69%
≥4	22	11,188	7,726	69%
≥5	7 (AU, CA, DK, ES, PT, UK, USA)	7,480	4,911	66%

≥6	5 (AU, ES, PT, UK, USA)	6,936	4,460	64%
≥7	4 (AU, ES, UK, USA)	6,805	4,353	64%
8	2 (UK, USA)	5,718	3,504	61%
Potentially OCS-related comorbidities				
≥1	22	11,809	7,936	67%
≥2	22	11,646	7,902	68%
≥3	22	11,489	7,865	68%
≥4	22	11,437	7,839	69%
≥5	22	11,427	7,834	69%
≥6	21 (all -DK)	11,043	7,654	69%
≥7	21 (all -DK)	11,034	7,647	69%
≥8	21 (all -DK)	11,027	7,643	69%
≥9	21 (all -DK)	11,015	7,634	69%
≥10	21 (all -DK)	10,932	7,575	69%
≥11	21 (all -DK)	10,823	7,491	69%
≥12	21 (all -DK)	10,365	7,149	69%
≥13	21 (all -DK)	9,892	6,876	70%
≥14	21 (all -DK, -IE)	9,660	6,744	70%
≥15	9 (AU, JP, MX, PL, SK, TW, UAE, UK, USA)	7,117	5,359	75%
≥16	3 (AU, UK, USA)	6,100	4,747	78%
17	3 (AU, UK, USA)	1,657	1,251	75%
Comorbidities mimicking/aggravating asthma				
≥1	7 (AU, CA, DK, ES, PT, UK, USA)	7,583	4,193	55%
≥2	7 (AU, CA, DK, ES, PT, UK, USA)	7,531	4,192	56%
≥3	7 (AU, CA, DK, ES, PT, UK, USA)	7,496	4,181	56%
≥4	6 (AU, CA, DK, ES, UK, USA)	7,259	4,136	57%
5	5 (AU, DK, ES, UK, USA)	7,136	4,106	58%

Abbreviations: AU: Australia; CN: Canada; DK: Denmark; ES: Spain; JP: Japan; MX: Mexico; PL: Portugal; PT: Portugal; SK: OCS: oral corticosteroids; SK: South Korea; TW: Taiwan; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America.

Prevalence of having 1, 2, or 3+ comorbidities

Prevalence estimates of having 3 or more comorbidities of any type ranged from 57% to 67%; 3 or more potentially T2-related comorbidities from 8.9% to 16%; 3 or more potentially OCS-related comorbidities from 23% to 34%; and 3 or more comorbidities mimicking/aggravating asthma from 3.9% to 4.1% (eTable 5). Of note, the trends were not linear due to variations in contributing countries as the minimum number of comorbidities with collected data increased.

eTable 5. Prevalence of having 1, 2, or 3+ comorbidities, overall and by categories, by minimum number of comorbidities with available presence/absence information.

Minimum number of comorbidities with presence/absence information by categories	Prevalence of having 1, 2, or 3+ comorbidities	Sample size	Number of contributing countries
Comorbidities of any type			
≥3	15%, 19%, 57%	11,794	22
≥4	15%, 19%, 58%	11,744	22
≥5	15%, 19%, 58%	11,683	22
≥6	15%, 19%, 58%	11,556	22
≥7	15%, 19%, 58%	11,468	22
≥8	15%, 19%, 58%	11,461	22
≥9	15%, 19%, 58%	11,455	22
≥10	15%, 19%, 58%	11,446	22
≥11	15%, 19%, 58%	11,438	22
≥12	15%, 19%, 59%	11,406	22
≥13	15%, 19%, 59%	11,388	22
≥14	15%, 19%, 59%	11,319	22
≥15	15%, 19%, 59%	11,120	22
≥16	15%, 19%, 58%	10,627	21 (all -Denmark)
≥17	15%, 19%, 58%	10,514	21 (all -Denmark)
≥18	15%, 18%, 59%	10,182	20 (all -Denmark, -Ireland)
≥19	13%, 16%, 63%	8060	12 (Australia, Canada, Japan, Mexico, Poland, Portugal, South Korea, Spain, Taiwan, UAE, UK, USA)
≥20	12%, 15%, 66%	7096	6 (Australia, Canada, Portugal, Spain, UK, USA)
≥21	12%, 15%, 66%	7088	6 (Australia, Canada, Portugal, Spain, UK, USA)
≥22	13%, 15%, 66%	7037	6 (Australia, Canada, Portugal, Spain, UK, USA)
≥23	13%, 16%, 65%	6909	6 (Australia, Canada, Portugal, Spain, UK, USA)
≥24	13%, 16%, 65%	6529	4 (Australia, Spain, UK, USA)
≥25	12%, 15%, 66%	6122	3 (Australia, UK, USA)
≥26	12%, 15%, 66%	6119	3 (Australia, UK, USA)
≥27	12%, 15%, 67%	6089	3 (Australia, UK, USA)
≥28	12%, 15%, 67%	6077	3 (Australia, UK, USA)
≥29	12%, 15%, 67%	5987	3 (Australia, UK, USA)
30	14%, 14%, 63%	1322	2 (UK, USA)
Potentially T2-related categories			
≥3	30%, 24%, 16%	11,623	22
≥4	30%, 23%, 16%	11,188	22
≥5	31%, 23%, 12%	7480	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)

≥6	32%, 22%, 11%	6936	5 (Australia, Portugal, Spain, UK, USA)
≥7	32%, 22%, 10%	6805	4 (Australia, Spain, UK, USA)
8	31%, 21%, 8.9%	5718	2 (UK, USA)
Potentially OCS-related comorbidities			
≥3	29%, 17%, 23%	11,489	22
≥4	28%, 17%, 23%	11,437	22
≥5	28%, 17%, 23%	11,427	22
≥6	28%, 17%, 24%	11,043	21 (all -Denmark)
≥7	28%, 17%, 24%	11,034	21 (all -Denmark)
≥8	28%, 17%, 24%	11,027	21 (all -Denmark)
≥9	28%, 17%, 24%	11,015	21 (all -Denmark)
≥10	28%, 17%, 24%	10,932	21 (all -Denmark)
≥11	28%, 17%, 24%	10,823	21 (all -Denmark)
≥12	28%, 17%, 24%	10,365	21 (all -Denmark)
≥13	28%, 17%, 25%	9892	21 (all -Denmark)
≥14	28%, 17%, 26%	9660	21 (all -Denmark, -Ireland)
≥15	26%, 18%, 31%	7117	9 (Australia, Japan, Mexico, Poland, South Korea, Taiwan, UAE, UK, USA)
≥16	26%, 18%, 34%	6100	3 (Australia, UK, USA)
17	28%, 15%, 32%	1657	3 (Australia, UK, USA)
Comorbidities mimicking/aggravating asthma			
≥3	35%, 17%, 3.9%	7496	7 (Australia, Canada, Denmark, Portugal, Spain, UK, USA)
≥4	36%, 17%, 4.0%	7259	6 (Australia, Canada, Denmark, Spain, UK, USA)
5	36%, 18%, 4.1%	7136	5 (Australia, Denmark, Spain, UK, USA)

UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America; OCS: Oral corticosteroids.

Most frequent comorbidities presenting alone and combinations of comorbidities

For each category of comorbidity counts (1, 2, and 3 or more), the most frequently reported individual, or combinations of, comorbidities are shown in eTable 6. In the categories of 3 or more comorbidities, the most frequent combinations of individual comorbidities were allergic rhinitis + chronic rhinosinusitis + nasal polyposis overall (6.4%). The most frequent combinations by categories were allergic rhinitis + chronic rhinosinusitis + nasal polyposis (55.5%) for potentially T2-related comorbidities, obesity + sleep apnea + hypertension (3.9%) for potentially OCS-related comorbidities, and gastro-esophageal reflux disease + chronic obstructive pulmonary disease + bronchiectasis (34.7%) for comorbidities mimicking/aggravating asthma.

eTable 6. Most frequent comorbidities and combinations of comorbidities by the number of reported comorbidities in patients with available presence/absence information for at least three comorbidities, overall and by categories.

Number of reported comorbidities	Sample size	Most frequent (combinations of) comorbidities		
		Types	N	(%)
Comorbidities of any type				
1	1811	Allergic rhinitis	672	(37.1)
		Obesity	511	(28.2)
		Chronic rhinosinusitis	123	(6.8)
2	2254	Allergic rhinitis + chronic rhinosinusitis	336	(14.9)
		Chronic rhinosinusitis + nasal polyposis	334	(14.8)
		Allergic rhinitis + obesity	287	(12.7)
3+	6761	Allergic rhinitis + chronic rhinosinusitis + nasal polyposis	430	(6.4)
		Allergic rhinitis + chronic rhinosinusitis + nasal polyposis + obesity	131	(1.9)
		Chronic rhinosinusitis + nasal polyposis + obesity	131	(1.9)
Potentially T2-related comorbidities				
1	3471	Allergic rhinitis	2,091	(60.2)
		Chronic rhinosinusitis	1,115	(32.1)
		Eczema/atopic dermatitis	169	(4.9)
2	2784	Allergic rhinitis + chronic rhinosinusitis	1,248	(44.8)
		Chronic rhinosinusitis + nasal polyposis	910	(32.7)
		Allergic rhinitis + eczema/atopic dermatitis	333	(12.0)
3+	1816	Allergic rhinitis + chronic rhinosinusitis + nasal polyposis	1,008	(55.5)
		Allergic rhinitis + chronic rhinosinusitis + eczema/atopic dermatitis	193	(10.6)
		Allergic rhinitis + chronic rhinosinusitis + nasal polyposis + eczema/atopic dermatitis	191	(10.5)
Potentially OCS-related comorbidities				
1	3276	Obesity	1,709	(52.2)
		Anxiety/depression	282	(8.6)
		Osteoporosis	249	(7.6)
2	1923	Obesity + sleep apnea	417	(21.7)
		Obesity + hypertension	156	(8.1)
		Obesity + anxiety/depression	155	(8.1)
3+	2666	Obesity + sleep apnea + hypertension	104	(3.9)
		Obesity + sleep apnea + diabetes	84	(3.2)
		Obesity + sleep apnea + hypertension + dyslipidaemia	52	(2.0)
Comorbidities mimicking/aggravating asthma				
1	2614	GERD	1,778	(68.0)
		COPD	327	(12.5)
		Bronchiectasis	248	(9.5)
2	1276	GERD + COPD	416	(32.6)
		GERD + vocal cord dysfunction/laryngeal spasms	388	(30.4)
		GERD + bronchiectasis	312	(24.5)
3+	291	GERD + COPD + bronchiectasis	101	(34.7)
		GERD + COPD + vocal cord dysfunction/laryngeal spasms	70	(24.1)
		GERD + bronchiectasis + vocal cord dysfunction/laryngeal spasms	37	(12.7)

COPD: Chronic obstructive pulmonary disease; GERD: Gastro-esophageal reflux disease; OCS: Oral corticosteroids.

Comorbidity prevalence by demographic characteristics

The prevalence of AR, eczema/atopic dermatitis, obesity, anxiety/depression, osteoporosis, diabetes, GERD, bronchiectasis, and vocal cord dysfunction/laryngeal spasms were higher in women than in men. By contrast, the prevalence of NP and sleep apnea was higher in men than in women **(eTable 7).** Patients with AR, NP, or eczema/atopic dermatitis were younger than those without these comorbidities**.** Conversely, those with obesity, hypertension, sleep apnea, dyslipidemia, anxiety/depression, osteoporosis, diabetes, GERD, COPD or bronchiectasis were older **(eTable 8)**. The relationship between comorbidities and smoking status (i.e. current, ex- or never smokers) was slightly more complicated **(eTable 9).** Potentially T2-relalted comorbidities were all more prevalent in never smokers (vs current/ex-smokers); obesity, hypertension, sleep apnea and GERD were more prevalent in ex-smokers (vs current or never smokers); and dyslipidemia, anxiety/depression, diabetes, and COPD were more prevalent in current/ex-smokers (vs never smokers).

eTable 7: Prevalence of the most common comorbidities by sex

Comorbidities	Women	Men	p value*
Potentially T2-related comorbidities			
Allergic rhinitis	50%	46%	0.003
Chronic rhinosinusitis[1]	45%	45%	0.893
Nasal polyposis	19%	24%	<0.001
Eczema/atopic dermatitis	10%	8.6%	0.006
Potentially OCS-related comorbidities			
Obesity	43%	36%	<0.001
Hypertension	22%	23%	0.249
Sleep apnea	21%	24%	0.003
Dyslipidaemia	16%	17%	0.156
Anxiety/depression[2]	17%	10%	<0.001
Osteoporosis	15%	6.7%	<0.001
Diabetes	12%	10%	0.007
Comorbidities mimicking/aggravating asthma			
GERD[3]	45%	42%	0.035
COPD	15%	16%	0.352
Bronchiectasis	11%	9.3%	0.027
VCD/laryngeal spasms	13%	6.6%	<0.001

[1]With or without nasal polyposis.

[2]Can also mimic/aggravate asthma.

[3]Can also be OCS-related.

*Pearson's Chi-squared test.

Abbreviations: COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; VCD: vocal cord dysfunction.

eTable 8: Prevalence of the most common comorbidities by age at registry enrollment

Comorbidities	<40	40-49	50-59	60-69	70+	p value*
Potentially T2-related categories						
Allergic rhinitis	56%	55%	48%	46%	40%	<0.001
Chronic rhinosinusitis[1]	39%	44%	48%	50%	40%	0.082
Nasal polyposis	20%	22%	26%	21%	15%	<0.001
Eczema/atopic dermatitis	16%	11%	7.8%	8.4%	7.6%	<0.001
Potentially OCS-related comorbidities						
Obesity	35%	41%	43%	43%	38%	0.007
Hypertension	5.0%	13%	20%	29%	40%	<0.001
Sleep apnea	11%	21%	24%	28%	27%	<0.001
Dyslipidemia	1.6%	8.0%	15%	21%	31%	<0.001
Anxiety/depression[2]	12%	11%	15%	16%	16%	<0.001
Osteoporosis	3.4%	4.5%	11%	17%	21%	<0.001
Diabetes	6.4%	7.8%	12%	14%	17%	<0.001
Comorbidities mimicking/aggravating asthma						
GERD[3]	34%	42%	42%	49%	48%	<0.001
COPD	3.0%	7.5%	17%	19%	23%	<0.001
Bronchiectasis	4.1%	6.8%	9.3%	13%	17%	<0.001
VCD/laryngeal spasms	11%	10%	11%	11%	8.7%	0.214

[1]With or without nasal polyposis.

[2]Can also mimic/aggravate asthma.

[3]Can also be OCS-related.

*Kruskal-Wallis rank sum test comparing age distributions in patients with versus without comorbidity.

Abbreviations: COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; VCD: vocal cord dysfunction.

eTable 9. Prevalence of most common comorbidities by smoking status registry enrollment.

Comorbidities	Current smokers	Ex-smokers	Never smokers	p value*
Potentially T2-related categories				
Allergic rhinitis	46%	42%	49%	<0.001
Chronic rhinosinusitis[1]	38%	43%	45%	0.012
Nasal polyposis	10%	16%	21%	<0.001
Eczema/atopic dermatitis	8.0%	7.5%	9.8%	0.007
Potentially OCS-related comorbidities				
Obesity	38%	47%	40%	<0.001
Hypertension	22%	29%	22%	<0.001
Sleep apnea	21%	31%	22%	<0.001
Dyslipidemia	19%	21%	16%	<0.001
Anxiety/depression[2]	21%	18%	13%	<0.001
Osteoporosis	6.1%	14%	12%	<0.001
Diabetes	14%	14%	12%	0.036
Comorbidities mimicking/aggravating asthma				
GERD[3]	45%	51%	45%	<0.001
COPD	42%	28%	7.4%	<0.001
Bronchiectasis	4.9%	11%	11%	0.017
VCD/laryngeal spasms	10%	11%	12%	0.668

1. With or without nasal polyposis.
2. Can also mimic/aggravate asthma.
3. Can also be OCS-related.

*Pearson's Chi-squared test.

Abbreviations: COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; VCD: vocal cord dysfunction.

Associations between individual comorbidities and clinical characteristics

eTable 10: Difference and 95% confidence intervals in age at asthma onset (in years) comparing patients with the respective comorbidity to those without it, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	Difference (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	4179	-2.95 (-3.98; -1.92)	<0.001
Chronic rhinosinusitis[1]	4225	+1.70 (+0.75; +2.64)	<0.001
Nasal polyposis	4463	+1.10 (+0.12; +2.08)	0.028
Eczema/atopic dermatitis	4449	-3.54 (-4.97; -2.11)	<0.001
Potentially OCS-related comorbidities			
Obesity	4435	-0.66 (-1.66; +0.34)	0.193
Hypertension	2816	+0.17 (-1.56; +1.90)	0.849
Sleep apnea	3342	-0.17 (-2.10; +1.76)	0.863
Dyslipidemia	1027	-0.12 (-8.20; +7.96)	0.977
Anxiety/depression[2]	4220	-0.87 (-2.39; +0.65)	0.261
Osteoporosis	3953	-0.49 (-2.09; +1.11)	0.552
Diabetes	4335	-1.94 (-3.63; -0.24)	0.025
Comorbidities mimicking/aggravating asthma			
GERD[3]	1258	-2.61 (-5.40; +0.17)	0.066
COPD	1318	-2.15 (-7.33; +3.03)	0.416
Bronchiectasis	1323	-2.07 (-5.54; +1.40)	0.243
VCD/laryngeal spasms	1133	-0.52 (-6.34; +5.31)	0.862

1. With or without nasal polyposis.

2. Can also mimic/aggravate asthma.

3. Can also be OCS-related.

*Wald's test.

Abbreviations: COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; VCD: vocal cord dysfunction.

eTable 11: Difference and 95% confidence intervals in blood eosinophil concentration (in cells/µL) comparing patients with the respective comorbidity to those without it, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	Difference (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	5594	+29.5 (+1.2; +57.9)	<0.001
Chronic rhinosinusitis[1]	5646	+158.9 (+131.8; +186.1)	<0.001
Nasal polyposis	5750	+200.9 (+166.7; +235.2)	<0.001
Eczema/atopic dermatitis	5727	+37.3 (-9.1; +83.6)	0.115
Potentially OCS-related comorbidities			
Obesity	5758	-63.4 (-91.2; -35.5)	<0.001
Hypertension	4490	-41.7 (-76.7; -6.7)	0.019
Sleep apnea	5046	-38.9 (-73.3; -4.5)	0.027
Dyslipidemia	3310	-6.0 (-47.4; +35.3)	0.775
Anxiety/depression[2]	5524	-43.7 (-80.4; -7.0)	0.020
Osteoporosis	5309	+43.2 (+1.8; +84.6)	0.041
Diabetes	5719	+3.23 (-36.9; +43.3)	0.875
Comorbidities mimicking/aggravating asthma			
GERD[3]	3582	-46.4 (-80.4; -12.4)	0.007
COPD	3625	-93.0 (-134.9; -51.1)	<0.001
Bronchiectasis	3633	+112.3 (+65.1; +159.5)	<0.001
VCD/laryngeal spasms	3492	-50.8 (-98.7; -3.0)	0.038

1. With or without nasal polyposis.

2. Can also mimic/aggravate asthma.

3. Can also be OCS-related.

*Wald's test.

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; VCD: vocal cord dysfunction.

eTable 12: Difference and 95% confidence intervals in blood IgE concentration (in IU/mL) comparing patients with the respective comorbidity to those without it, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	Difference (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	4591	+100.3 (+50.3; +150.2)	<0.001
Chronic rhinosinusitis[1]	4723	-5.6 (-53.3; +42.1)	0.812
Nasal polyposis	4849	-20.7 (-79.7; +38.3)	0.492
Eczema/atopic dermatitis	4837	+271.2 (+191.9; +350.4)	<0.001
Potentially OCS-related comorbidities			
Obesity	4845	-47.9 (-96.8; +1.0)	0.055
Hypertension	3723	-14.7 (-82.2; 52.8)	0.669
Sleep apnea	4246	-67.0 (-130.8; -3.2)	0.039
Dyslipidemia	2790	-73.0 (-154.7; +8.6)	0.080
Anxiety/depression[2]	4611	-51.4 (-118.7; +15.8)	0.134
Osteoporosis	4400	+36.7 (-38.0; +111.3)	0.336
Diabetes	4759	-43.8 (-116.8; +29.3)	0.240
Comorbidities mimicking/aggravating asthma			
GERD[3]	3018	-58.1 (-120.9; +4.7)	0.070
COPD	3050	+4.8 (-74.9; +84.5)	0.905
Bronchiectasis	3055	+114.4 (+30.8; +198.0)	0.007
VCD/laryngeal spasms	2928	-65.0 (-154.7; +24.7)	0.156

1. With or without nasal polyposis.

2. Can also mimic/aggravate asthma.

3. Can also be OCS-related.

*Wald's test.

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; VCD: vocal cord dysfunction.

eTable 13. Difference and 95% confidence intervals in FeNO test result (in ppb) comparing patients with the respective comorbidity to those without it, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	Difference (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	3423	+5.4 (+2.1; +8.7)	0.001
Chronic rhinosinusitis[1]	3453	+12.6 (+9.5; +15.7)	<0.001
Nasal polyposis	3554	+17.7 (+14.0; +21.5)	<0.001
Eczema/atopic dermatitis	3551	-1.5 (-6.7; +3.7)	0.573
Potentially OCS-related comorbidities			
Obesity	3550	-9.3 (-12.4; -6.2)	<0.001
Hypertension	3043	-7.6 (-11.7; -3.5)	<0.001
Sleep apnea	3100	-7.2 (-11.2; -3.2)	<0.001
Dyslipidemia	2298	-7.8 (-13.3; -2.3)	0.005
Anxiety/depression[2]	3308	-5.8 (-10.0; -1.5)	0.008
Osteoporosis	3115	-3.9 (-8.8; +0.9)	0.114
Diabetes	3472	-6.8 (-11.8; -1.9)	0.007
Comorbidities mimicking/aggravating asthma			
GERD[3]	2498	-7.4 (-11.6; -3.3)	<0.001
COPD	2530	-11.7 (-17.1; -6.2)	<0.001
Bronchiectasis	2535	-5.5 (-11.2; +0.2)	0.059
VCD/laryngeal spasms	2456	-1.8 (-7.5; +3.9)	0.537

1. With or without nasal polyposis.

2. Can also mimic/aggravate asthma.

3. Can also be OCS-related.

*Wald's test.

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; FeNO: fractional exhaled nitric oxide; GERD: gastroesophageal disease; OCS: oral corticosteroids; ppb: parts per billion; VCD: vocal cord dysfunction.

Associations between individual comorbidities and asthma-related outcomes

eTable 14: Association between the most common comorbidities and receiving long-term OCS at registry enrollment: odds ratios and 95% confidence intervals of receiving long-term OCS associated with presence of comorbidities, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	OR (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	7976	0.97 (0.86-1.10)	0.653
Chronic rhinosinusitis[1]	8020	1.46 (1.30-1.64)	<0.001
Nasal polyposis	8271	1.40 (1.22-1.60)	<0.001
Eczema/atopic dermatitis	8255	0.87 (0.71-1.06)	0.172
Potentially OCS-related comorbidities			
Obesity	8252	1.12 (1.00-1.27)	0.057
Hypertension	6452	1.33 (1.13-1.56)	<0.001
Sleep apnea	7058	1.23 (1.04-1.46)	0.014
Dyslipidemia	4465	1.48 (1.18-1.86)	<0.001
Anxiety/depression[2]	7894	1.42 (1.21-1.66)	<0.001
Osteoporosis	7661	2.77 (2.35-3.27)	<0.001
Diabetes	8139	1.39 (1.17-1.66)	<0.001
Comorbidities mimicking/aggravating asthma			
GERD[3]	4831	1.51 (1.27-1.80)	<0.001
COPD	4900	1.18 (0.95-1.48)	0.132
Bronchiectasis	4906	1.57 (1.26-1.96)	<0.001
VCD/laryngeal spasms	4668	1.37 (1.06-1.77)	0.016

1. With or without nasal polyposis.
2. Can also mimic/aggravate asthma.
3. Can also be OCS-related.

*Wald's test.

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; OR: odds ratio; VCD: vocal cord dysfunction.

eTable 15: Association between the most common comorbidities and exacerbation rates at registry enrollment: ratios of means and 95% confidence intervals of number of exacerbations in the year preceding enrollment associated with presence of comorbidities, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	Ratio of means (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	7060	1.12 (1.04-1.21)	0.003
Chronic rhinosinusitis[1]	7036	1.29 (1.21-1.38)	<0.001
Nasal polyposis	7283	1.16 (1.07-1.25)	<0.001
Eczema/atopic dermatitis	7265	1.11 (0.99-1.23)	0.072
Potentially OCS-related comorbidities			
Obesity	7278	1.04 (0.97-1.11)	0.254
Hypertension	5699	1.15 (1.03-1.28)	0.015
Sleep apnea	6390	1.09 (0.99-1.20)	0.072
Dyslipidemia	4233	1.21 (1.04-1.40)	0.013
Anxiety/depression[2]	6971	1.40 (1.28-1.54)	<0.001
Osteoporosis	6734	1.61 (1.45-1.79)	<0.001
Diabetes	7181	1.07 (0.96-1.19)	0.233
Comorbidities mimicking/aggravating asthma			
GERD[3]	4519	1.68 (1.50-1.87)	<0.001
COPD	4573	1.38 (1.21-1.58)	<0.001
Bronchiectasis	4578	1.36 (1.17-1.57)	<0.001
VCD/laryngeal spasms	4427	1.24 (1.06-1.45)	0.008

1. With or without nasal polyposis.

2. Can also mimic/aggravate asthma.

3. Can also be OCS-related.

*Wald's test.

Abbreviations: COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OCS: oral corticosteroids; VCD: vocal cord dysfunction.

eTable 16: Association between the most common comorbidities and lung function at registry enrollment: averaged differences and 95% confidence intervals of post-bronchodilator FEV_1 percent predicted at enrollment associated with presence of comorbidities, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	Average difference (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	6061	3.16 (2.02;4.30)	<0.001
Chronic rhinosinusitis[1]	6139	2.22 (1.14;3.30)	<0.001
Nasal polyposis	6230	1.86 (0.45;3.27)	0.010
Eczema/atopic dermatitis	6206	1.80 (-0.09;3.68)	0.062
Potentially OCS-related comorbidities			
Obesity	6288	-0.52 (-1.61;0.57)	0.347
Hypertension	5000	-2.64 (-4.08;-1.20)	<0.001
Sleep apnea	5561	0.82 (-0.54;2.19)	0.235
Dyslipidemia	3768	-0.43 (-2.23; 1.38)	0.643
Anxiety/depression[2]	5974	-0.74 (-2.21;0.73)	0.326
Osteoporosis	5747	-3.42 (-5.06;-1.77)	<0.001
Diabetes	6167	-3.54 (-5.13;-1.96)	<0.001
Comorbidities mimicking/aggravating asthma			
GERD[3]	4036	0.10 (-1.31;1.50)	0.892
COPD	4076	-15.9 (-17.6;-14.2)	<0.001
Bronchiectasis	4081	-5.24 (-7.32;-3.16)	<0.001
VCD/laryngeal spasms	3955	4.82 (2.78;6.85)	<0.001

1. With or without nasal polyposis.
2. Can also mimic/aggravate asthma.
3. Can also be OCS-related.

*Wald's test.

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; FEV_1: forced expiratory volume in 1 second; VCD: vocal cord dysfunction.

eTable 17: Odds ratio and 95% confidence intervals of having asthma uncontrolled at enrollment associated with presence of comorbidities, adjusted for country, age at registry enrollment, and sex.

Comorbidities	Sample size	OR (95% CI)	p value*
Potentially T2-related categories			
Allergic rhinitis	4722	0.95 (0.83-1.09)	0.436
Chronic rhinosinusitis[1]	4701	0.91 (0.79-1.03)	0.140
Nasal polyposis	4930	0.91 (0.78-1.06)	0.222
Eczema/atopic dermatitis	4917	1.22 (0.99-1.51)	0.063
Potentially OCS-related comorbidities			
Obesity	4945	1.47 (1.29-1.69)	<0.001
Hypertension	3646	1.38 (1.15-1.65)	<0.001
Sleep apnea	4088	1.59 (1.32-1.92)	<0.001
Dyslipidemia	2333	0.93 (0.72-1.20)	0.575
Anxiety/depression[2]	4697	1.68 (1.40-2.02)	<0.001
Osteoporosis	4454	1.29 (1.05-1.57)	0.015
Diabetes	4862	1.31 (1.06-1.60)	0.011
Comorbidities mimicking/aggravating asthma			
GERD[3]	2530	1.81 (1.48-2.23)	<0.001
COPD	2578	1.57 (1.22-2.03)	<0.001
Bronchiectasis	2585	1.08 (0.80-1.46)	0.613
VCD/laryngeal spasms	2494	1.81 (1.38-2.37)	<0.001

1. With or without nasal polyposis.

2. Can also mimic/aggravate asthma.

3. Can also be OCS-related.

*Wald's test.

Abbreviations: CI: confidence interval; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal disease; OR: odds ratio; VCD: vocal cord dysfunction.

eReferences.

1. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. Res Synth Methods. 2019;10(3):476-483.

2. Bulathsinhala L, Eleangovan N, Heaney LG, Menzies-Gow A, Gibson PG, Peters M, et al. Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study. J Allergy Clin Immunol Pract. 2019;7:578-588.e2.

3. Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, et al. Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. Chest. 2021;160:814–30.