LUNGER I PRAKSIS

MEDLEMSBLAD

02

APRIL 2023

Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update

One-minute sit-to-stand test as a quick functional test for people with COPD in general practice

Predictive and prognostic value of leptin status in asthma

The feasibility and impact of implementing a computer-guided consultation to target health inequality in Asthma

Addressing sex and gender to improve asthma management

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International Primary Care IPCRG Respiratory Group

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Oslo, april 2023

Kjære kollega,
Snart vår!

Astmaveileder for allmennpraksis
Lunger i praksis har fulgt opp kolsveileder for allmennpraksis med en astmaveileder. Vi har ikke noen oppdaterte veiledere for astma i Norge, noe som vi syntes ikke er holdbart. Det har skjedd mye siden NFA kom med sin i 2015. Veilederen kan du får ved henvendelse til oss.

Lungekurs Trondheim 9. - 11. mars 2023
Kurset i lungesykdommer på Britannia hotell i Trondheim ble en stor suksess! Det var over 130 deltager og gledelig at over 40 var medarbeidere!! Gode diskusjoner og mye interaktivitet preget kurset. Vi kommer tilbake til Trondheim i 2024 – samme sted!!

Lungedagene Oslo 8. – 11. november 2023
Neste mulighet for kurs blir i Oslo på Lungedagene 2023. Vi holder kurset som vanlig på Clarion Hotel Oslo, sentralt og kun et steinkast fra Sentralbanestasjonen. Som vanlig, to emnekurs fra onsdag til lørdag – og som alltid, medarbeiderkurs fra torsdag kveld til lørdag. Sett av tiden nå, mer nyheter kommer!!

IPCRG
IPCRG`s neste forskningsmøte blir i München i år, datoer er nå bekreftet til 15. og 16. mai, kanskje ikke helt ideelt for oss norske – men hvorfor ikke få litt faglig påfyll før det fylle på med pølser og is på 17. mai? Neste verdenskongress blir i Hellas i 9. - 11. mai 2024. Se også mye nyttig informasjon på IPCRG`s hjemmeside; www.theIPCRG.org

Medlemsfordeler
Mange av deltagerne på våre kurs ønsker presentasjoner fra kursene til bruk lokalt. Dette er mulig som medlem av Lip, i tillegg sender vi gjerne våre oppdaterte «Kliniske råd» til bruk i for eksempel smågrupper!
Nytt; vi har utarbeidet egne presentasjoner på astma og kols som egner seg godt til smågrupper! Ta kontakt så sender vi dem på mail! Vi har følgende kliniske råd; Spirometri, Årskontroll for astma og kols, Røykavvenning, Astma, Allergi, Kols og en for medarbeidere.
Ta kontakt på mail; anders.ostrem@outlook.com

Vennlig hilsen
Styret

LUNGEDAGENE 2023
8. - 11. NOVEMBER
CLARION HOTEL OSLO

I år ønsker vi velkommen til hovedstaden og to emnekurs. Lungedagene er som et kinder-egg, godt faglig utbytte, mange kurspoeng og hyggelig ramme sosialt for hele kontoret. Som vanlig vil vi ha medarbeiderkurs, så det er bare å ta med hele kontoret til Oslo.

Begge kurs er godkjent som kliniske emnekurs, hvert med 16 timer/poeng.
Link til informasjon og påmelding kommer snart!

Vi var strålende fornøyd med vårt nye faste konferanse-hotell i fjor så vi har plass der i år også. Clarion Hotel Oslo, ligger kun noen få minutters gange fra Oslo sentralstasjon. Ved eventuelle spørsmål om kursene, ta kontakt med Knut Weisser Lind; kwlind@online.no

LHLs digitale kolsskole

Tekst: Helle S. Grøttum, LHL Astma og allergi

Et gratis tilbud for alle med kols, deres pårørende, fagfolk og alle interesserte. Kolsskolen skal bidra til økt kunnskap og livsmestring for personer med kols og deres pårørende. Den digitale skolen består av fire moduler/filmer. I kolsskolen møter du en brukerrepresentant, som deler sine opplevelser om å få kols. Han forteller om hvordan han lever med kols og håndterer hverdagen på godt og vondt. Spesialist i lungesykdommer, sykepleier, fysioterapeut, ernærings-fysiolog, psykolog, ergoterapeut og pasientombud bidrar med sin kompetanse og gir råd om å leve best mulig med sin lungesykdom.

Den digitale kolsskolen er en god kilde til kunnskap, også om en har fått opplæring hos egen lege, i sykehus eller har vært på lungere-habilitering. Innholdet er en god blanding av fag og erfaringsbasert stoff. Den er gratis og lett tilgjengelig på nett, og passer for alle uansett fysiske forutsetninger og hvor i landet man bor.

LHL håper fastleger som møter kolspasienter vil henvise til kolsskolen som kilde til informasjon. Det er laget små blokker med QR-kode og kort presentasjon av kolsskolen. Disse fås gratis ved henvendelse til prosjektleder Helle S. Grøttum, helle.grottum@lhl.no

Fysioterapeut Ulla Pedersen fra LHL viser Jan Frode Hagstrøm styrkeøvelser.
Foto: Sanden Media

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I DETTE NUMMERET

Vi begynner denne gangen med en oversikt over oppdateringer i de siste GINA retningslinjer som er relevant for allmennpraksis. GINA er en internasjonal astmaveileder som skal omfavne hele verden. Lunger i praksis publiserte høsten 2022 en praktisk astmaveileder for fastleger som i stor grad følger GINA, men som også har viktige forskjeller. GINA kom med en svært viktig endring i 2019 da man anbefalte ICS-formoterol som behandling fra trinn 1 for pasienter > 12 år. Dette er videreført og stemmer godt overens med vår norske veileder. Det er spesielt for barn mellom 6 og 12 år man finner forskjeller, vi anbefaler samme behandlingstrapp til denne gruppen som for pasienter over 12 år. GINA legger også vekt på å stille riktig diagnose ved å bruke objektiv lungefunksjonsundersøkelse som spirometri. Spirometri er heldigvis tilgjengelig hos alle fastleger i Norge. Et annet viktig poeng GINA presiserer er at hos pasienter som ikke har optimal kontroll (kalles ofte «difficult to manage» astma) er faktorer som bedret etterlevelse og inhalasjonsteknikk viktig å følge opp. Kommer man ikke til mål med en strukturert gjennomgang bør pasienten henvises til spesialisthelsetjenesten. Lunger i praksis sin veileder finner du på våre hjemmesider.

I neste artikkel av J.G. Spenc og medarbeidere fra Danmark tar man opp et viktig tema; hvordan vurdere fysisk yteevne hos kolspasienter i en travel allmennpraksis? Internasjonale retningslinjer anbefaler ofte tester som er krevende å utføre, både med tanke på tidsbruk og plass. I studien intervjuet man 64 helsearbeidere fra primærhelsetjenesten for å finne ut om en enkel test (1 minutts sitte og stå test, 1M STST) vil være aktuell å bruke – og ikke minst – om det var mulig å implementere den (altså ta den i bruk). Mange kjenner nok ikke til 1M STST i Norge, men testen er svært enkel. Man måler hvor mange ganger en kolspasient klarer å sette og reise seg fra en stol på ett minutt. Den endring på +/- 3 repetisjoner mellom to tester er klinisk relevant for pasienten. Svarene i undersøkelsen var entydige, testen var rask å gjennomføre og kunne implementeres ved årskontroller. For at vi skal klare å samle nyttig informasjon fra våre pasienter er vi helt avhengig av at undersøkelser og tester er så «tidseffektive» som mulig – 1M STST er derfor nyttig å bruke!

I neste artikkel, av Juan Wang og medarbeidere fra Kina, så man på studier som undersøkte om nivå av leptin hadde sammenheng med astma. Man ønsket å kartlegge nærmere om leptin kunne være et signal for alvorlig astma og i hvilken grad det kunne forutsi utvikling av sykdommen. Så kan du gjerne spørre om hvordan et hormon som frigjøres fra lipopcytter skal kunne si noe om astma! Leptin sin hovedfunksjon er å kontrollere vekt igjennom å styre appetitt og energiforbruk. Men det har også pro-inflammatoriske egenskaper og det er vist at økt nivå er assosiert med økt bronkial hyperreaktivitet, som jo er sentralt hos pasienter med astma. Når forfatterne samlet data fra mange studier viste det seg at astmapasienter hadde høyere nivå av leptin og at nivået korrelerte med alvorlighetsgraden av sykdommen. Imidlertid så man forskjeller mellom ulike etniske grupper. Selv om forfatterne mener leptin vil være nyttig, vil det nok ta tid før analysen blir inkludert som standard. Men det er en spennende tanke om vi kan følge astmapasientenes sykdomsutvikling med en blodprøve.

Det er mye fokus på bruk av datastøtteverktøy både i medisinen og i samfunnet ellers. Vi har tidligere omtalt artikler som ser på beslutningsstøtte verktøy innen allmennpraksis. I studien til B. Chakrabarti og medarbeidere fra Storbritannia undersøkte man om bruken av et slikt verktøy (Clinical Decision Support System – CDSC) kunne bedre oppfølgingen av pasienter med astma. Man brukte verktøyet som ledd i et kvalitetsprosjekt der målet var å bedre oppfølging og redusere overforbruk av SABA (korttidsvirkende beta2 agonister). Ved å søke i legenes journalsystem hentet man ut informasjon om medisinbruk, forverringer og om pasienten hadde vært til systematisk gjennomgang. Pasientene ble så invitert til en strukturert gjennomgang på legekontoret der man brukte et CDSS for å strukturere kontrollen. Resultatene viste at mange pasienter med dårlig astmakontroll ble identifisert, noe som førte til endring av medisiner hos 44% av pasientene. Hovedsakelig fikk pasientene økt behandlingen. Så ved å bruke et datastøtteverktøy ble kvaliteten av behandlingen økt. I Norge bruker mange Medrave som et verktøy for å jobbe med kvalitet på legekontoret – det har vist seg nyttig og nye programmer kommer nok som kan hjelpe oss enda bedre.

Den siste artikkelen til Louis-Philippe Boulet og medarbeidere er en oversiktsartikkel om hvordan vi kan ta hensyn til kjønnsforskjeller i behandlingen av astma. Jeg skal ikke forsøke å summere hele artikkelen, men vi vet at mye påvirker sykdommen, ikke bare hormoner, men også forskjellige utløsende faktorer. God lesing!

Hørte du klikket?

Med et klikk fra NEXThaler kan du være sikker på at hele dosen har blitt avgitt[1–3]

INHALASJONSKLIKKET som høres når dosen frigjøres, sørger for at pasienten kan føle seg trygg på at inhalatoren håndteres korrekt.

Hvis pasienten har åpnet inhalatoren, men lukker beskyttelseslokket uten å ha inhalert, går dosen tilbake til pulverbeholderen, slik at neste dose kan inhaleres sikkert.

Det er først etter at pasienten faktisk har inhalert dosen – og inhalatoren har klikket – at inhalasjonstelleren registrerer dosen.

Trimbow®
NEXThaler®
beklometasondipropionat/
formoterolfumaratdihydrat/
glykopyrronium
INHALASJONSKLIKKET

Referanser: 1. Trimbow pulverinhalator (NEXThaler) SmPC, 2022. **2.** Buttini F, Brambilla G, Copelli D, et al. Effect of Flow Rate on In Vitro Aerodynamic Performance of NEXThaler in Comparison with Diskus and Turbohaler Dry Poweder Inhalers. J Aerosol Med Pulm Drug Deliv. 2016;29:167–17. **3.** Corradi M, Chrystyn H, Cosio B G, et al. NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclomethasone and formoterol to treat large and small airways in asthma. Expert Opin Drug Deliv. 2014;11:1497–1506.

Trimbow (beklometasondipropionat, formoterolfumaratdihydrat og glykopyrronium) Inhalasjonspulver 88 µg/5 µg/9 µg. **Indikasjon:** Vedlikeholdsbehandling hos voksne med moderat til alvorlig kronisk obstruktiv lungesykdom (kols), som ikke er adekvat behandlet med en kombinasjon av et inhalert kortikosteroid og en langtidsvirkende ß2-agonist eller en kombinasjon av en langtidsvirkende ß2-agonist og en langtidsvirkende muskarinantagonist (for effekt på symptomkontroll og forebygging av eksaserbasjoner, se SPC pkt. 5.1.). **Dosering:** 2 inhalasjoner 2 ganger daglig. Pasienten må instrueres i riktig inhalasjonsteknikk. **Pakninger og pris (AUP):** *Nexthaler inhalator:* 1×120 doser: kr 714,40. 3×120 doser: 2056,80. **Refusjonsberettiget bruk:** Vedlikeholdsbehandling ved kols, iht. preparatomtale. *ICPC/ICD:* R95/J44: Kronisk obstruktiv lungesykdom/Annen kronisk obstruktiv lungesykdom. Vilkår: Ingen spesifisert. **Reseptgruppe:** C.

Utvalgt sikkerhetsinformasjon

- Ikke indisert til behandling av akutt bronkospasme eller akutt sykdomseksaserbasjon.
- Risiko for paradoksal bronkospasme (må behandles umiddelbart), pneumoni hos kolspasienter, alvorlig hypokalemi, kardiovaskulære effekter, systemiske kortikosteroideffekter, hyperglykemi, vinkelblokkglaukom, urinretensjon, synsforstyrrelser og umiddelbar overfølsomhetsreaksjon.
- Forsiktighet skal utvises ved alvorlig nedsatt nyre- eller leverfunksjon, hjertearytmier, idiopatisk subvalvulær aortastenose, hypertrofisk obstruktiv kardiomyopati, alvorlig hjertesykdom, okklusiv karsykdom, arteriell hypertensjon, aneurisme, forlenget QTc-intervall, tyreotoksikose, diabetes mellitus, feokromocytom, ubehandlet hypokalemi, aktiv/latent tuberkulose, sopp- og virusinfeksjon i luftveiene, vinkelblokkglaukom, prostatahyperplasi og urinretensjon.
- Ved liten effekt eller sykdomseksaserbasjon, bør behandlingen revurderes. Bør ikke seponeres brått.
- Ved bruk av flere bronkodilatatorer som anfallsmedisin, bør serumkaliumnivået overvåkes.
- *Interaksjoner:* Må ikke gis samtidig med ikke-kardioselektive betablokkere eller samtidig med/de siste 12 timer før halogenerte anestetika. Langvarig samtidig bruk av andre antikolinergika anbefales ikke. Forsiktighet utvises ved samtidig bruk av potente CYP3A-hemmere, andre beta-adrenergika, legemider som kan gi hypokalemi, legemidler som påvirker nyreutskillelsesmekanismer, samtidig bruk med kinidin, disopyramid, prokainamid, antihistaminer, MAO-hemmere, TCA og fenotiaziner (gir økt risiko for ventrikulære arytmier), samt ved bruk av L dopa, L tyroksin, oksytocin og alkohol (kan hemme hjertetoleransen).
- *Graviditet og amming:* Bruk under graviditet og fødsel bør unngås. Ved inntak av anselige doser hos mor, må barnet observeres for adrenalsuppresjon. Det må besluttes om amming skal opphøre eller behandling avstås fra.
- *Bivirkninger:* Hyppigst sett er dysfoni, oral candidose, muskelspasmer og munntørrhet.

For utfyllende informasjon om dosering, kontraindikasjoner, advarsler og forsiktighetsregler, interaksjoner og bivirkninger, se Trimbow SPC godkjent 24.03.2022.

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REVIEW ARTICLE OPEN

Check for updates

Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update

Mark L. Levy[1]✉, Leonard B. Bacharier[2], Eric Bateman[3], Louis-Philippe Boulet[4], Chris Brightling[5], Roland Buhl[6], Guy Brusselle[7,8], Alvaro A. Cruz[9], Jeffrey M. Drazen[10], Liesbeth Duijts[11], Louise Fleming[12], Hiromasa Inoue[13], Fanny W. S. Ko[14], Jerry A. Krishnan[15], Kevin Mortimer[16,17,18], Paulo M. Pitrez[19], Aziz Sheikh[20], Arzu Yorgancıoğlu[21] and Helen K. Reddel[22]

The Global Initiative for Asthma (GINA) was established in 1993 by the World Health Organization and the US National Heart Lung and Blood Institute to improve asthma awareness, prevention and management worldwide. GINA develops and publishes evidence-based, annually updated resources for clinicians. GINA guidance is adopted by national asthma guidelines in many countries, adapted to fit local healthcare systems, practices, and resource availability. GINA is independent of industry, funded by the sale and licensing of its materials. This review summarizes key practical guidance for primary care from the 2022 GINA strategy report. It provides guidance on confirming the diagnosis of asthma using spirometry or peak expiratory flow. GINA recommends that all adults, adolescents and most children with asthma should receive inhaled corticosteroid (ICS)-containing therapy to reduce the risk of severe exacerbations, either taken regularly, or (for adults and adolescents with "mild" asthma) as combination ICS–formoterol taken as needed for symptom relief. For patients with moderate–severe asthma, the preferred regimen is maintenance-and-reliever therapy (MART) with ICS–formoterol. Asthma treatment is not "one size fits all"; GINA recommends individualized assessment, adjustment, and review of treatment. As many patients with difficult-to-treat or severe asthma are not referred early for specialist review, we provide updated guidance for primary care on diagnosis, further investigation, optimization and treatment of severe asthma across secondary and tertiary care. While the GINA strategy has global relevance, we recognize that there are special considerations for its adoption in low- and middle-income countries, particularly the current poor access to inhaled medications.

npj Primary Care Respiratory Medicine (2023)33:7 ; https://doi.org/10.1038/s41533-023-00330-1

INTRODUCTION

Asthma affects more than a quarter of a billion people worldwide, is the most common chronic condition in childhood, and is responsible for over 1000 deaths a day, of which the majority are preventable[1–4].

The Global Initiative for Asthma (GINA) was established by the World Health Organization and the US National Heart Lung and Blood institute in 1993 to improve asthma awareness, prevention, and management worldwide. GINA is independent of industry, funded by the sale and licensing of its evidence-based, annually updated reports and figures. The GINA methodology is published on its website (https://ginasthma.org/about-us/methodology).

The GINA report is a global evidence-based strategy that can be adapted for local health systems and local medicine availability. Many countries have their own national asthma guidelines, with many of these based on GINA[5]. However, most national guidelines are updated only infrequently, so they may not reflect current best evidence. In recent years, some countries have conducted partial updates of their asthma guidelines, by undertaking a detailed review of evidence for a limited number of clinical questions, but this process often takes several years. By contrast, the GINA strategy is updated every year based on a twice-yearly cumulative review of new evidence. Hence, even when national asthma guidelines are available, the GINA report may provide a useful resource for clinicians (both primary care and specialists) to be aware of the most recent evidence, and to understand how it can be integrated into holistic asthma care. However, when assessing and treating patients, health professionals are strongly advised to use their own professional judgment, and to take into account local and national regulations and guidelines, and the needs of the individual patient.

While the GINA strategy report is intended to have global relevance, there are particular considerations for asthma management in low- and middle-income countries[6,7]. Of particular concern is the widespread lack of access to affordable diagnostic tools and inhaled medications, which contributes substantially to

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Table 1. Summary of changes in the 2022 GINA Strategy Report of particular relevance to primary care.

Topic or section	Changes
Diagnosis of asthma	Diagnostic testing is different depending on whether the patient is already on controller treatment or is treatment-naive or taking SABA alone (see Tables 2 and 3). Detail has been included about diagnosis and management of asthma in low-resource settings
Assessment of symptom control	When assessing symptom control, record how often the patient is using their reliever inhaler (ICS–formoterol or SABA). For patients prescribed a SABA reliever, use of SABA more than two days a week should prompt review of their adherence and inhaler technique with their maintenance controller treatment. This criterion does not apply to patients using an ICS–formoterol reliever, as it is providing additional controller treatment along with the symptom relief. Dispensing of three or more SABA canisters a year (more than average 1.5 puffs/day) is associated with increased risk of severe exacerbations, and may be associated with increased risk of asthma death
Definition of mild asthma	GINA suggests that the term 'mild asthma' should generally be avoided in clinical practice where possible, because patients often assume that it means they do not need any controller treatment. However, if the term is used, explain to the patient that patients with apparently mild asthma can still have severe attacks, and that using ICS-containing treatment, especially with ICS–formoterol reliever, will markedly reduce this risk
GINA treatment figure for adults and adolescents	The rationale for showing two treatment tracks has been reinforced: Track 1, with as-needed ICS–formoterol as reliever across treatment steps, is preferred based on evidence for lower risk of exacerbations and similar or better symptom control compared with using SABA as reliever
Treatment figure for children 6–11 years	The figure has been updated to explain the "other controller options" and new Step 5 options for this age group
Adding LAMA to ICS-LABA for adults and adolescents (Step 5)	Patients with exacerbations despite ICS-LABA should receive at least medium dose ICS-LABA before considering add-on LAMA
Difficult-to-treat and severe asthma in adults and adolescents	The GINA Guide and decision tree for assessment and management of difficult-to-treat and severe asthma in adults and adolescents has been revised and enlarged. Additional investigations have been suggested for patients with difficult-to-treat asthma and blood eosinophils ≥300/μL, including investigating for non-asthma causes such as Strongyloides, which is often asymptomatic. New biologic treatment options have been approved for severe asthma and are available in many countries, so referral to a specialist is recommended if asthma is poorly controlled despite Step 4 treatment
Maintenance oral corticosteroids—consider only as last resort	Because of the risk of serious long-term adverse effects, maintenance OCS should be considered only as a last resort in any age group
Written asthma action plans (handwritten, printed, digital, or pictorial)	Give patients documented instructions about how to change their medications when their asthma worsens, and when to seek medical advice. Verbal instructions are often forgotten
Management of wheezing episodes in pre-school children	In children ≤5 years with intermittent viral wheezing and no or few interval respiratory symptoms, consideration of intermittent short-course ICS has been added to the treatment figure. It should be considered only if the physician is confident that it will be used appropriately, because of the risk of side effects
Management of acute asthma in healthcare settings	After an Emergency Department visit or hospitalization, make sure patients are returned to as-needed (rather than regular) reliever use. For patients using ICS–formoterol as their reliever, make sure that they switch back to this after any acute healthcare presentation

Modified with permission from ref. [11].
ICS inhaled corticosteroid, *LABA* long-acting beta$_2$ agonist, *LAMA* long-acting muscarinic antagonist, *SABA* short-acting beta$_2$ agonist, *OCS* oral corticosteroid.

the heavy burden of asthma mortality and morbidity seen in these countries.

At the most fundamental level, patients in many areas do not have access even to low-dose inhaled corticosteroids (ICS), which are the cornerstone of care for asthma patients of all severity.

GINA collaborates with and strongly supports the call by the International Union against Tuberculosis and Lung Diseases for a World Health Assembly Resolution on universal access to affordable and effective asthma care, as a step towards addressing these needs[8].

GINA is also a partner organization in a program launched in March 2006 by the World Health Organization (WHO) and the Global Alliance against Chronic Respiratory Diseases (GARD). Through the work of GINA, and in co-operation with GARD and with the International Union Against Tuberculosis and Lung Diseases, substantial progress toward better care for all patients with asthma globally should be achieved in the next decade.

To achieve this, GINA believes that the safest and most effective approach to asthma treatment in adolescents and adults, which also avoids the consequences of starting treatment with short-acting beta$_2$ agonists (SABA) alone, depends on access to ICS–formoterol across all asthma severity levels. With budesonide-formoterol now on the WHO essential medicines list[9], the fundamental changes to treatment of mild asthma first included in the ground-breaking 2019 GINA report[10] may provide a feasible solution to reduce the risk of severe exacerbations with very low dose treatment.

In this review we discuss four key concepts for asthma management in primary care: diagnosis, long-term treatment, assessment of control, and management of severe asthma. We provide the background to the latest (May 2022) update of the GINA strategy report[11], with a focus on changes (Table 1) and selected recommendations that are particularly pertinent to primary care practitioners, and their rationale. The full strategy

Table 2. Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years.

1. HISTORY OF VARIABLE RESPIRATORY SYMPTOMS	
Feature	*Symptoms or features that support the diagnosis of asthma*
Wheeze, shortness of breath, chest tightness and cough (Descriptors may vary between cultures and by age)	• More than one type of respiratory symptom (in adults, isolated cough is seldom due to asthma) • Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms often appear or worsen with viral infections
2. CONFIRMED VARIABLE EXPIRATORY AIRFLOW LIMITATION	
Feature	*Considerations, definitions, criteria*
2.1 Documented* expiratory airflow limitation	At a time when FEV_1 is reduced, confirm that FEV_1/FVC is reduced compared with the lower limit of normal (it is usually >0.75–0.80 in adults, >0.90 in children)
AND	
2.2 Documented* excessive variability in lung function* (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis. If initially negative, tests can be repeated during symptoms or in the early morning.
• Positive bronchodilator (BD) responsiveness (reversibility) test	*Adults*: increase in FEV_1 of >12% and >200 mL (greater confidence if increase is >15% and >400 mL). *Children*: increase in FEV_1 by >12% predicted Measure change 10–15 min after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥ 4 h, twice-daily LABA 24 h, once-daily LABA 36 h
• Excessive variability in twice-daily PEF over 2 weeks	*Adults*: average daily diurnal PEF variability >10%[a] *Children*: average daily diurnal PEF variability >13%[a]
• Significant increase in lung function after 4 weeks of anti-inflammatory treatment	*Adults*: increase in FEV_1 by >12% and >200 mL (or PEF^2 by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
• Positive exercise challenge test	*Adults*: fall in FEV_1 of >10% and >200 mL from baseline *Children*: fall in FEV_1 of >12% predicted, or PEF >15%
• Positive bronchial challenge test (usually only for adults)	Fall in FEV_1 from baseline of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
• Excessive variation in lung function between visits (good specificity but poor sensitivity)	*Adults*: variation in FEV_1 of >12% and >200 mL between visits, outside of respiratory infections *Children*: variation in FEV_1 of >12% in FEV_1 or >15% in PEF[b] between visits (may include respiratory infections)

Source: Box 1–2 in GINA 2022. Reproduced with permission from ref. [11].
BD bronchodilator (SABA or rapid-acting LABA), *FEV_1* forced expiratory volume in 1 s, *ICS* inhaled corticosteroid, *LABA* long-acting $beta_2$ agonist, *PEF* peak expiratory flow (highest of three readings), *SABA* short-acting $beta_2$ agonist.
[a]Daily diurnal PEF variability is calculated from twice daily PEF as (day's highest minus day's lowest) divided by (mean of day's highest and lowest), averaged over 1 week.
[b]Use the same PEF meter each time, as PEF may vary by up to 20% between different meters.

documents, podcasts, educational materials, and summary booklets are available on the GINA website (https://ginasthma.org).

DIAGNOSIS OF ASTHMA

It is critical to confirm the diagnosis of asthma

Primary care clinicians are consulted by patients with many hundreds of different medical conditions in any year. Every day, they are faced with the challenge of quickly arriving at an accurate diagnosis in limited time, and often with limited access to specialized investigations.

In order to ensure diagnosis of asthma is considered as early as possible, clinicians should maintain a high index of suspicion when patients present with respiratory symptoms[12].

Over- and under-diagnosis of asthma are common and are usually due to the lack of objective lung function testing which can demonstrate variable expiratory airflow limitation that will support the diagnosis of asthma and help to exclude other causes[13,14]. For continuity of care, it is important to ensure that the diagnosis is recorded in each patient's medical record, detailing the basis for the diagnosis, including objective measurements of variable airflow obstruction and airway inflammation, if available. These details are often lacking in the medical records of children[15] and adults treated for asthma[16,17].

Medical records should also contain details of treatment prescribed, education given to help patients understand the chronic nature of their disease, and provision of a personal written action plan to enable them to change their treatment and seek assistance when needed.

Diagnosing asthma in adults, adolescents and children aged 6–11 years

Confirm the diagnosis of asthma before starting controller treatment, if possible: There is no single test for confirming the diagnosis of asthma. First, a clinical diagnosis starts with a history of respiratory symptoms (such as cough, wheeze, difficulty breathing and/or shortness of breath) that typically vary over time and intensity (Table 2 and Fig. 1). Symptoms of asthma are often worse at night and in the early morning, and may be triggered by factors such as viral infections, allergen exposure, exercise, strong smells, cigarette smoke, exhaust fumes and laughter. When taking a history, it may be helpful to show patients or carers a video depicting typical symptoms, such as the one developed by Wellington School of Medical and Health Sciences, University of Otago, New Zealand, available from the Global Asthma Network website (http://globalasthmanetwork.org/

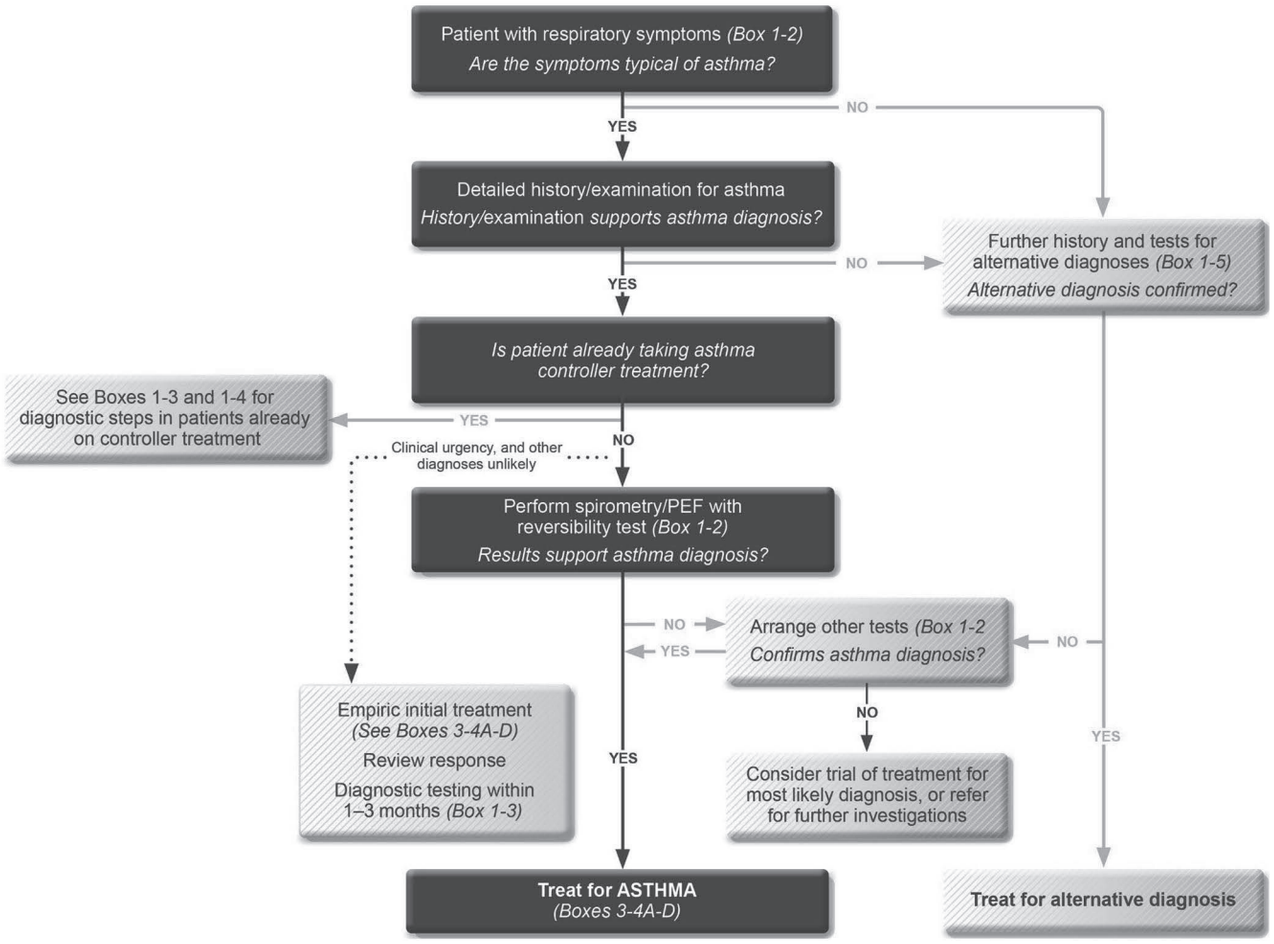

Fig. 1 The GINA diagnostic flowchart 2022. PEF peak expiratory flow. Source: Box 1–1 in GINA report 2022. Box numbers within the figure refer to the GINA 2022 report. Reproduced with permission from ref. [11].

surveillance/manual/Asthma_AVQ3.1.mp4). Physical examination may be entirely normal.

Variable expiratory airflow limitation is the other cardinal feature of untreated asthma. In a patient with a history suggestive of asthma, the diagnosis of asthma is supported by an increase in forced expiratory volume in 1 s (FEV_1) recorded by spirometry 15 min after administration of bronchodilator: in adults/adolescents, by an increase of more than 200 mL and 12% from the pre-bronchodilator (baseline) FEV_1; in children, by an increase from baseline of more than 12% of the predicted FEV_1 value.

Since asthma is a variable condition, bronchodilator reversibility (also called responsiveness) may or may not be present at the time of initial lung function testing. If it is not documented on spirometry at an initial attempt, the test should be repeated at one or more later visits, preferably when the patient is symptomatic and bronchodilator medicines have been withheld. Otherwise, an alternative test may be conducted (as below and in Table 2).

Spirometry is not always accessible in primary care. An alternative method is to instruct the patient to record peak expiratory flow (PEF) each morning and evening over a 2-week period in a diary or using an electronic peak flow meter. PEF should be measured three times on each occasion, and only the highest reading used. Diurnal PEF variability is calculated as each day's highest minus the day's lowest reading, divided by the mean of the day's highest and lowest, then these results are averaged over one week. Excessive diurnal PEF variability is defined as a mean variability of >10% in PEFs in adults or >13% variability in children. When measuring PEF, the same meter should be used for all readings, as variation between different PEF meters may be as large as 20%.

In people with suspected asthma who have normal expiratory airflow and no significant reversibility, a bronchoprovocation test (e.g., methacholine or mannitol) can reveal airway hyperresponsiveness, supporting a diagnosis of asthma. Bronchodilators must be withheld before challenge testing.

Variable expiratory airflow limitation should preferably be demonstrated before initiating asthma controller treatment, except in situations of clinical urgency, as it becomes harder to confirm the diagnosis once controller treatment has been started (Table 3). However, the diagnosis of asthma can also be confirmed if there is a clinically significant improvement in FEV_1 (by >12% and >200 mL) or in PEF by >20% after 4 weeks of inhaled corticosteroid (ICS) treatment.

A history or family history of allergic rhinitis or atopic dermatitis, or the presence of atopy (demonstrated by either a positive skin prick test or specific IgE to one or more aeroallergens) increases the chance that a patient with respiratory symptoms has allergic asthma, but these features are not specific for asthma, and asthma may be non-allergic.

Evidence of Type 2 inflammation (for example, fractional exhaled nitric oxide [FeNO] >25 ppb or blood eosinophils >300/μL) is found in some types of asthma, but also in several non-asthma conditions such as allergic rhinitis and eosinophilic bronchitis. Therefore, the presence or absence of these biomarkers

Table 3. Steps for confirming the diagnosis of asthma in a patient already taking controller treatment.

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2–2) and review controller treatment (Box 3–5).
Variable respiratory symptoms but no variable airflow limitation	Consider repeating spirometry after withholding BD (4 h for SABA, 24 h for twice-daily ICS-LABA, 36 h for once-daily ICS-LABA) or during symptoms. Check between-visit variability of FEV_1, and bronchodilator responsiveness. If still normal, consider other diagnoses (Box 1–5). *If FEV_1 is >70% predicted*: consider stepping down controller treatment (see Box 1–5) and reassess in 2–4 weeks, then consider bronchial provocation test or repeating BD responsiveness. *If FEV_1 is <70% predicted*: consider stepping up controller treatment for 3 months (Box 3–5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation.
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Consider repeating BD responsiveness test again after withholding BD as above or during symptoms. If normal, consider alternative diagnoses (Box 1–5). Consider stepping down controller treatment (see Box 1–5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to previous lowest effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing controller, and monitor patient closely for at least 12 months (Box 3–7).
Persistent shortness of breath and persistent airflow limitation	Consider stepping up controller treatment for 3 months (Box 3–5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap (Chapter 5).

"Variable airflow limitation" refers to expiratory airflow. GINA recommendations for confirming the diagnosis in those already started on controller treatment. Source: Box 1–3 in GINA 2022. Box and chapter numbers refer to the GINA 2022 report. Reproduced with permission from ref. [11].
BD bronchodilator, *COPD* chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume in 1 s, *ICS* inhaled corticosteroid, *LABA* long-acting $beta_2$ agonist, *SABA* short-acting $beta_2$ agonist.

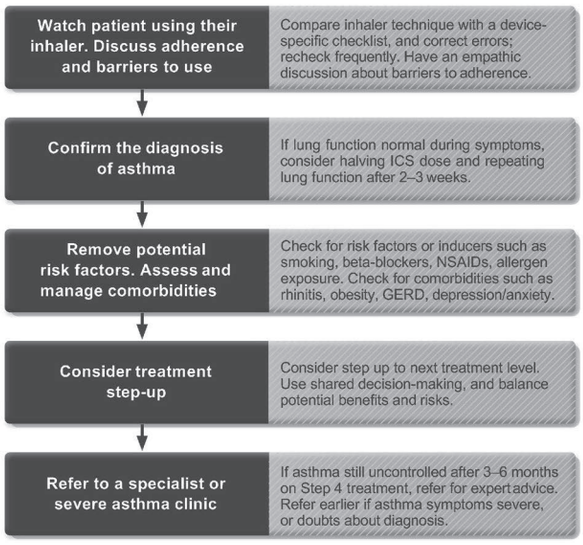

Fig. 2 Investigating poor symptom control and/or exacerbations despite treatment. ICS inhaled corticosteroid, NSAID nonsteroidal anti-inflammatory drug, GERD gastro-esophageal reflux disease. Reproduced with permission from ref. [11].

cannot confirm or exclude a diagnosis of asthma, particularly if measured after starting ICS treatment. However, in patients with severe asthma, FeNO and blood eosinophils are useful to select and guide treatment.

If symptoms persist or are more typical of an alternative diagnosis, or if the patient experiences no benefit after commencement of controller therapy, the diagnosis should be reviewed, and alternative causes of the symptoms should be considered (Fig. 2).

Consider occupational asthma in patients presenting with adult-onset asthma: Occupational asthma should be considered in anyone newly presenting in adulthood with symptoms suggestive of asthma, particularly if there is improvement when away from work. If occupational asthma is suspected, early referral to a specialist (if available) is important, to assist with assessment of the person's work environment and confirm the diagnosis. Exposure to the sensitizing agent should cease if at all possible, because ongoing exposure to even low levels can lead to severe problems. The specialist may be able to assist with negotiation with employers to reduce/cease exposure and, where relevant, with recommendations for compensation in accordance with applicable local employment laws. Patients with adult-onset asthma should also be asked about exposure to sensitizers or irritants in non-work locations, e.g., use of cleaning agents at home, or hobbies such as woodworking.

Persistent airflow obstruction may develop over time—so it is important to differentiate asthma from chronic obstructive pulmonary disease (COPD): The history and pattern of symptoms and past records can help to distinguish asthma with persistent airflow limitation from COPD. Asthma and COPD may co-exist in the same patient, particularly in smokers and the elderly.

It is important to recognize features of asthma in these patients because anti-inflammatory treatment with ICS is essential in asthma (whether or not there are also features of COPD such as persistent airflow limitation) to prevent severe flare-ups (severe exacerbations) and reduce the risk of asthma-related death. Figure 3 summarizes features that are useful in distinguishing asthma from COPD.

Diagnosing asthma in children aged 5 years and under. It can be challenging to make the diagnosis of asthma in some children aged ≤5 years. Recurrent wheezing is very common in this age group, including in children without asthma, typically with viral upper respiratory tract infections. Routine assessment of airflow limitation or bronchodilator responsiveness in this age group is difficult and is not practical in primary care.

Asthma diagnosis in children aged ≤5 years can be based on symptom patterns, the presence of risk factors, therapeutic response to controller treatment, and exclusion of alternative diagnoses: A

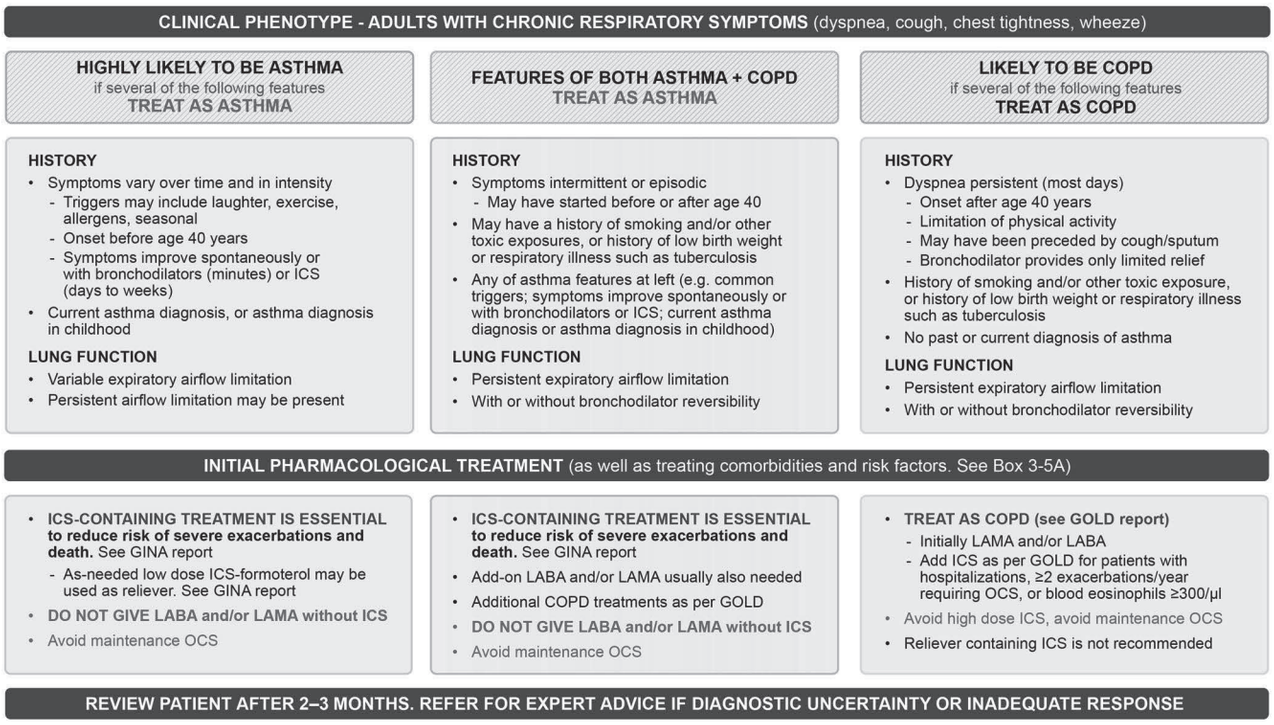

Fig. 3 Approach to initial treatment in patients with asthma and/or COPD. GOLD Global Initiative for Obstructive Lung Disease, ICS inhaled corticosteroid, LABA long-acting β_2 agonist; LAMA long-acting muscarinic antagonist. A summary of differentiating and diagnostic features in people with Asthma, COPD and Asthma + COPD. Source: Box 5–2 in GINA 2022. Reproduced with permission from ref. [11].

diagnosis of asthma in young children with a history of wheezing is more likely if they have wheezing or coughing that occurs with exercise, laughing or crying, or in the absence of an apparent respiratory infection, a history of other allergic disease (eczema, food allergy, or allergic rhinitis), atopy or asthma in first-degree relatives, clinical improvement during 2–3 months of controller treatment, and worsening after cessation.

The following questions can be used to elicit features suggestive of asthma in young children and features that help support the diagnosis:

- Does your child have wheezing? Wheezing is a high-pitched noise that comes from the chest and not the throat. Use of a video questionnaire, or asking a parent to record an episode on a smartphone if available can help to confirm the presence of wheeze and differentiate from upper airway abnormalities.
- Does your child wake up at night because of coughing, wheezing, or difficult breathing, heavy breathing, or breathlessness?
- Does your child have to stop running, or play less hard, because of coughing, wheezing or difficult breathing, heavy breathing, or shortness of breath?
- Does your child cough, wheeze or get difficult breathing, heavy breathing, or shortness of breath when laughing, crying, playing with animals, or when exposed to strong smells or smoke?
- Has your child ever had eczema, or been diagnosed with allergy to foods?
- Has anyone in your close family had asthma, hay fever, food allergy, eczema, or any other disease with breathing problems?

In preschool children with wheeze, phenotypes have been proposed based on short-term symptom patterns[18] or on symptom pattern trends over time[19–21], but these have not proved to be clinically useful or accurate in predicting asthma in later childhood.

LONG-TERM TREATMENT OF ASTHMA

All patients diagnosed with asthma should be treated with ICS-containing medication

GINA recommends that all adults, adolescents and children over 5 years with a diagnosis of asthma should be treated with regular or (for mild asthma) as-needed ICS-containing treatment to control symptoms and prevent flare-ups (also called exacerbations or "attacks"), and that they should be reviewed within three months after initiating and/or changing treatment. In children ≤5 years, ICS treatment is recommended if asthma is likely and the child has uncontrolled symptoms and/or ≥3 wheezing episodes/year; a trial of ICS is also recommended if the diagnosis is uncertain and symptoms occur more than every 6–8 weeks.

GINA recommends against treating asthma with SABA alone, without ICS

GINA no longer recommends treatment of asthma with SABA alone (without ICS) in adults, adolescents and children >5 years (Figs. 4–6) because of the risk of severe asthma flare-ups (severe exacerbations) requiring emergency department presentation or hospitalization, and asthma-related death. These risks are markedly reduced by ICS-containing therapy[22,23]. Treating with ICS also substantially reduces the need for courses of oral corticosteroids, thereby reducing the cumulative risk of long-term adverse effects such as osteoporosis and cataract from even occasional courses of oral corticosteroids[24]. A further reason to avoid treating asthma with SABA alone is because their quick symptom relief may instill a false sense of security in patients, who may incorrectly assume that these medicines alone are a sufficient treatment for asthma.

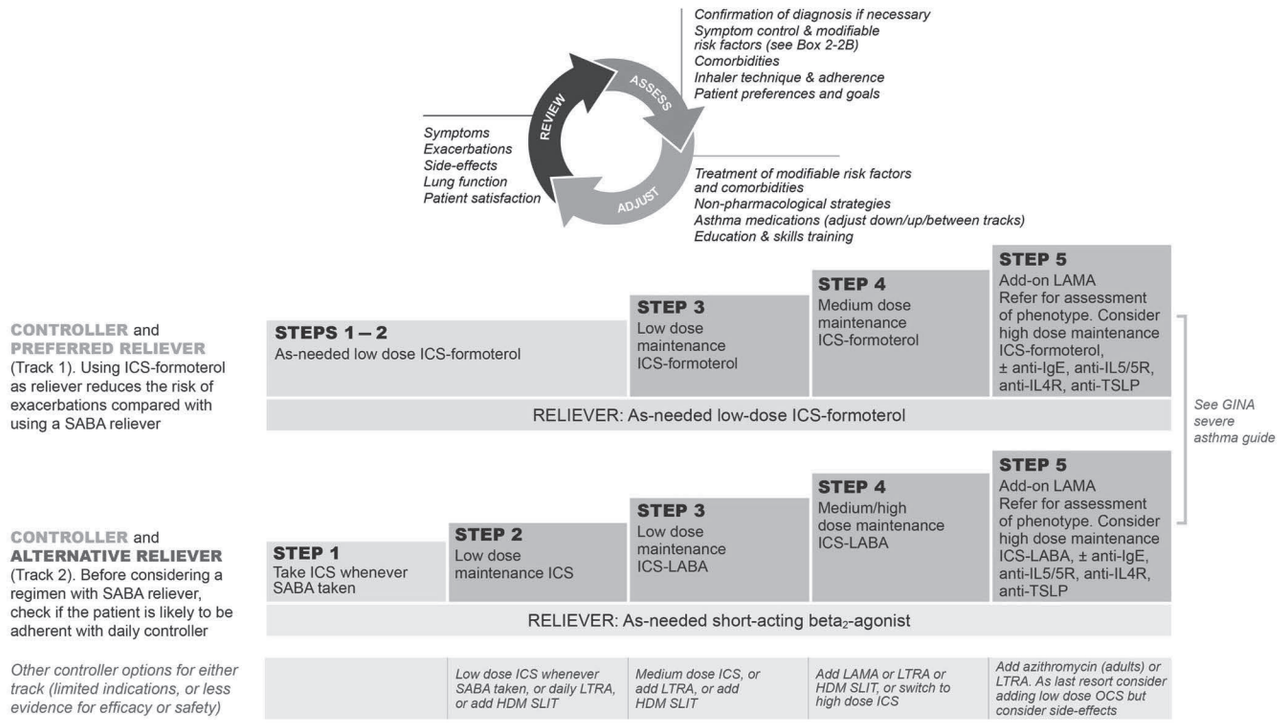

Fig. 4 Two-track options for personalized management of asthma for adults and adolescents, to control symptoms and minimize future risk. HDM house dust mite, ICS inhaled corticosteroid, LABA long-acting beta$_2$ agonist, LAMA long-acting muscarinic antagonist, LTRA leukotriene receptor antagonist, OCS oral corticosteroids, SABA short-acting beta$_2$ agonist, SLIT sublingual immunotherapy. Box number refers to the GINA 2022 report. Before starting, stepping up or down or switching between tracks, patients should be assessed using the "assess, adjust, review" cycle shown at the top of the figure. Refer to the GINA report for more information about Step 5 options, including biologic therapies for patients with severe asthma. Source: Box 3–5A in GINA report 2022. Reproduced with permission from ref. [11].

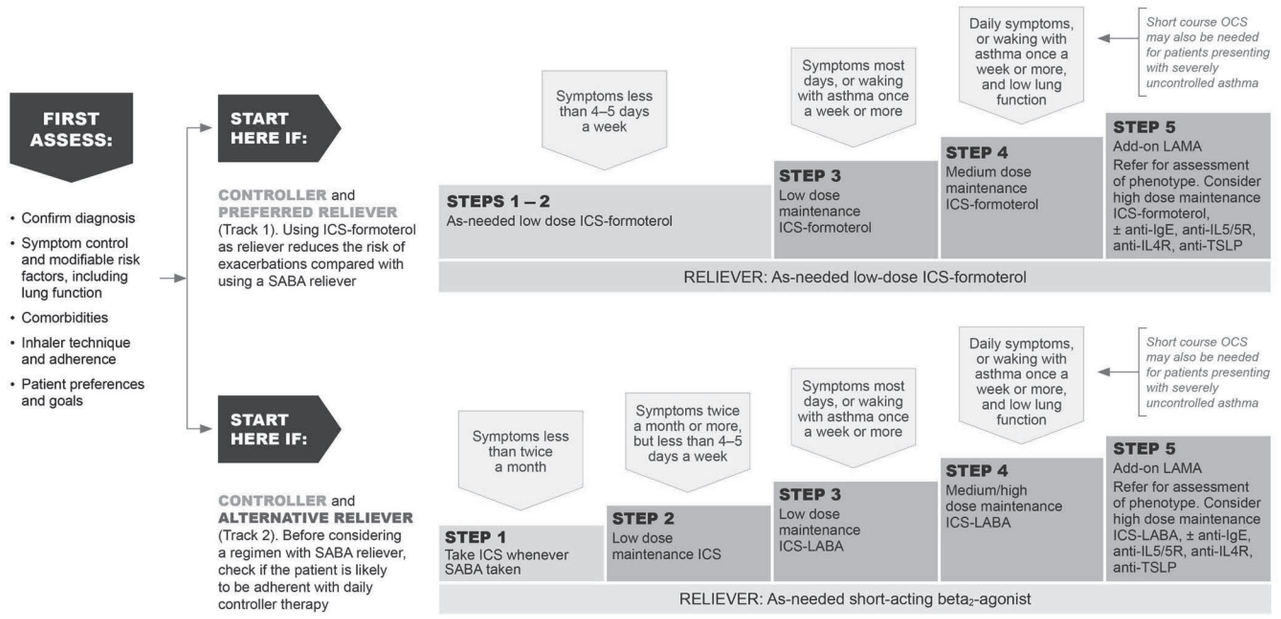

Fig. 5 Initial medications for adults and adolescents diagnosed with asthma. ICS inhaled corticosteroid, LABA long-acting beta$_2$ agonist, LAMA long-acting muscarinic antagonist, MART maintenance and reliever therapy with ICS–formoterol, OCS oral corticosteroids, SABA short-acting beta$_2$ agonist. Initial medications for adults and adolescents diagnosed with asthma, with guidance on initial levels of medication for each treatment track based on symptoms and lung function where appropriate. Refer to the GINA report for other treatment components, including treatment of modifiable risk factors and comorbidities, non-pharmacologic strategies, and education and skills training. Source: Box 3.4Bi in GINA report 2022. Reproduced with permission from ref. [11].

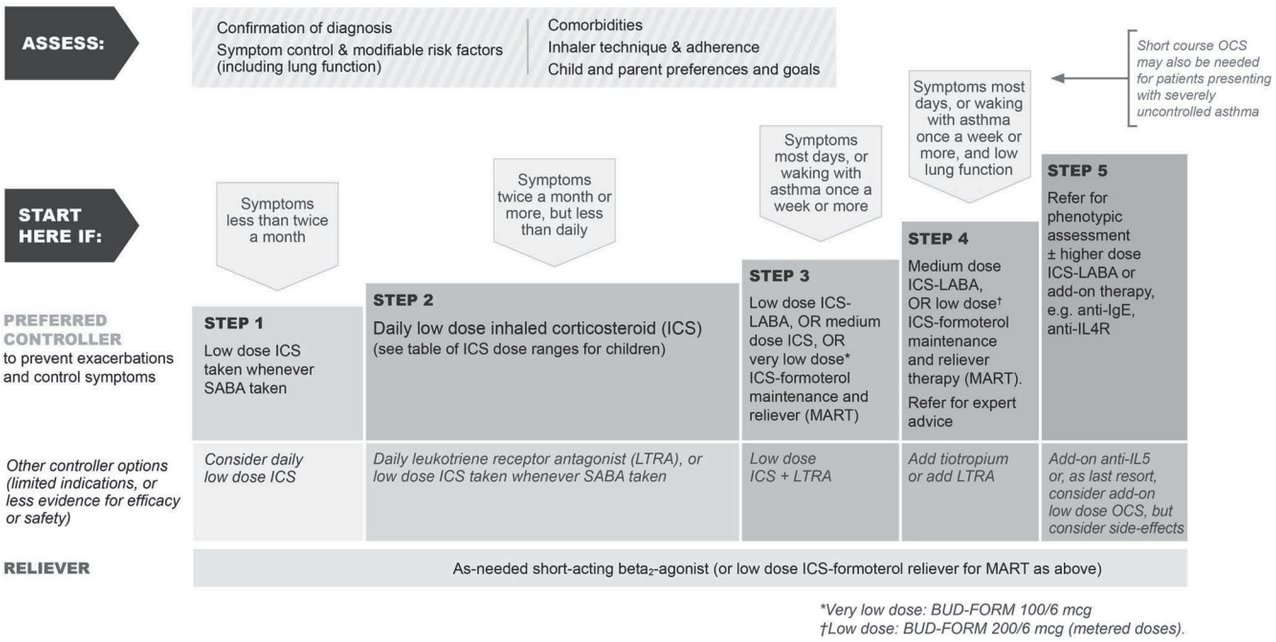

Fig. 6 Initial medications for children aged 6–11 years diagnosed with asthma. BUD-FORM budesonide–formoterol, ICS inhaled corticosteroid, LABA long-acting beta$_2$ agonist, LTRA leukotriene receptor antagonist, MART maintenance and reliever therapy with ICS–formoterol, OCS oral corticosteroids, SABA short-acting beta$_2$ agonist. Initial treatment for children aged 6–11 years diagnosed with asthma, with guidance on initial levels of medication for each treatment track based on symptoms and lung function where appropriate. Source: Box 3–4Di in GINA report 2022. Refer to the GINA report for other treatment components, including treatment of modifiable risk factors and comorbidities, non-pharmacologic strategies, and education and skills training. Reproduced with permission from ref. [11].

In addition, regular use of SABA (e.g., 2–4 times daily for as little as 1–2 weeks) increases airway hyperresponsiveness and airway inflammation[25,26], and overuse of SABA (indicated by dispensing of ≥3 200-dose canisters in a year, or daily use), is associated with an increased risk of severe exacerbations and death, even in patients also taking ICS[27–29].

Compared with as-needed SABA, as-needed low-dose ICS–formoterol for symptom relief reduces the risk of severe asthma flare-ups (severe exacerbations) across all levels of asthma severity—either as-needed only in mild asthma or in addition to maintenance ICS–formoterol

GINA's current recommendations for the pharmacotherapy of asthma in adults and adolescents are shown in two 'tracks' (Figs. 4–5). There is strong evidence favoring the Track 1 option, in which low-dose ICS–formoterol is the reliever across all treatment steps, compared with Track 2, in which SABA is the reliever[23,30–39].

This recommendation is based on multiple studies demonstrating that combination low-dose ICS and formoterol, taken as-needed for relief of asthma symptoms (either as-needed only in mild asthma, or in addition to maintenance ICS–formoterol), is a more effective and safer reliever than as-needed SABA.

In patients with mild asthma, as-needed ICS–formoterol reduces the risk of severe flare-ups by 60–64% compared with as-needed SABA[36,37]. Compared with low-dose maintenance ICS plus as-needed SABA, the risk of severe exacerbations is similar[35–38]. In a Cochrane systematic review and meta-analysis ($n = 9565$), patients with mild asthma treated with as-needed ICS–formoterol had a 55% reduction in severe exacerbations and 65% lower emergency department visits or hospitalizations compared with SABA alone. In addition, those treated with as-needed ICS–formoterol had 37% lower risk of emergency department visits or hospitalizations than with daily ICS plus as-needed SABA[23]. In some of these studies, there were small differences in lung function (FEV_1) and symptom control assessed by Asthma Control Questionnaire (ACQ-5) score that favored daily maintenance ICS over as-needed-only low-dose ICS–formoterol. These differences were not clinically important, and may reflect that adherence with maintenance ICS was much higher than is usually achievable in clinical practice. The average daily dose of ICS was much lower with as-needed ICS–formoterol compared with daily ICS plus as-needed SABA.

Further, in patients with moderate-to-severe asthma (Steps 3 and 4, Figs. 4–5), use of ICS–formoterol as both maintenance and reliever therapy (MART) in Track 1 reduces the risk of severe flare-ups (severe exacerbations), compared with taking the same or higher dose of ICS or a combination of ICS and a long-acting beta$_2$ agonist (LABA) plus SABA reliever[30,31]. In Steps 3 and 4, symptom control and lung function with MART are the same or better compared with use of a SABA reliever.

Although Track 1 is preferred because of the significant reduction in severe exacerbations, Track 2 (with SABA as reliever) is an alternative option if ICS–formoterol is not available or if patients have no risk factors for exacerbations and have good adherence with regular controller therapy. However, before prescribing Track 2 therapy with a SABA reliever, the clinician should assess whether the patient is likely to continue to be adherent with daily controller treatment, as otherwise they will be taking SABA alone, with an increased risk of severe exacerbations.

At the time of publishing, over 45 countries have licensed ICS–formoterol for as-needed use in mild asthma and over 120 countries have licensed prescription of MART in moderate-to-severe asthma (personal communications). Detailed practical advice on the implementation of MART in clinical practice has recently been published[40,41], including downloadable resources (ICS–formoterol dosing and SMART action plan).

GINA asthma treatment is not "one size fits all"

Because asthma is a chronic condition prone to flare-ups, GINA emphasizes that patients need regular review, assessment and adjustment. This involves assessment of asthma control, individual

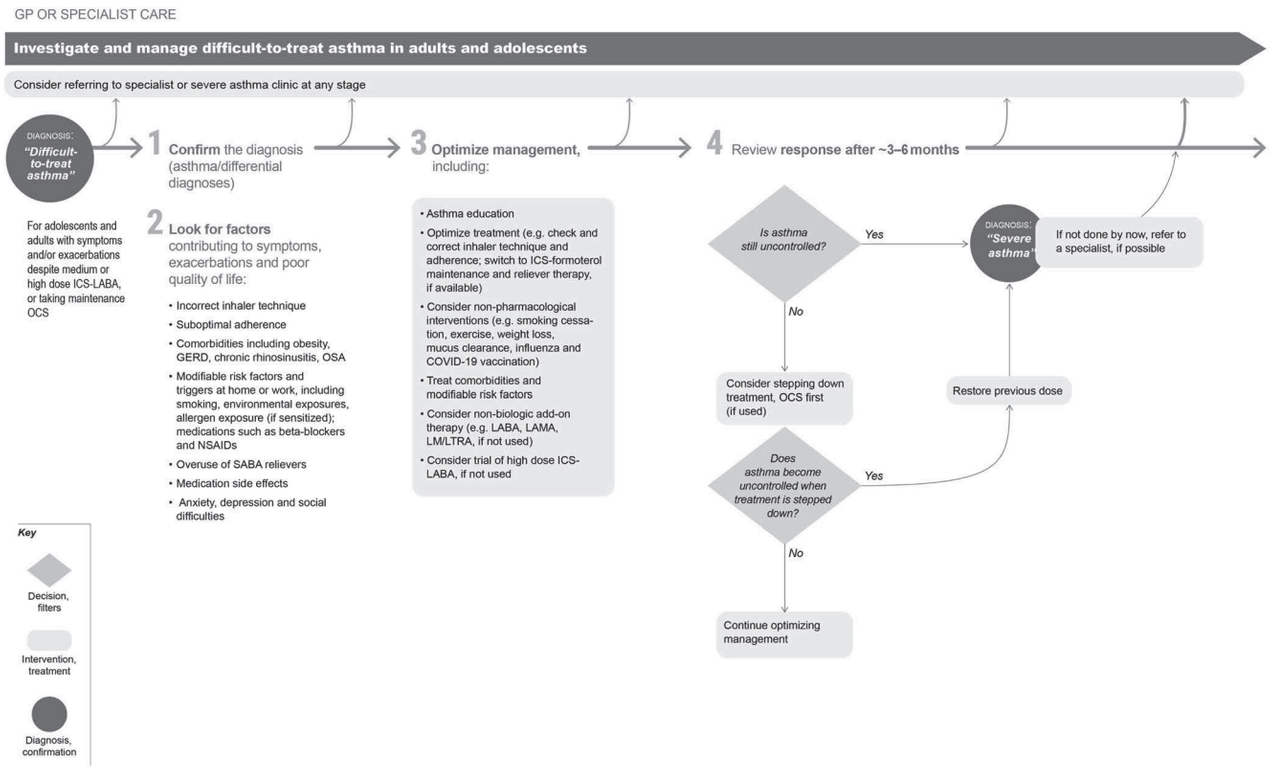

Fig. 7 Investigating and managing difficult-to-treat asthma in adult and adolescent patients. ICS inhaled corticosteroid, LABA long-acting beta$_2$ agonist, LAMA long-acting muscarinic antagonist, LTRA leukotriene receptor antagonists, SABA short-acting beta$_2$ agoinst, OCS oral corticosteroid. The GINA strategy includes a decision tree about the management of difficult-to-treat and severe asthma spanning primary through tertiary care. The section of the flow diagram applicable to generalists in primary and secondary care is shown here. Source: Box 3–16A in GINA report 2022. Reproduced with permission from ref. [11].

risk factors and comorbidities, with review and optimization of treatment, including careful attention to adherence and inhaler technique, and provision of individualized self-management education including a written/pictorial action plan.

Management of co-morbid conditions that may worsen asthma control, increase the risk of severe flare-ups and/or complicate treatment should be optimized. These comorbidities include obesity, chronic rhinosinusitis, obstructive sleep apnea, gastro-esophageal reflux disease, and mental health problems (Fig. 7).

Treatment should be reviewed after any flare-ups or changes in treatment (Fig. 2). The components of these assessments are summarized in the personalized asthma management cycle (Assess, Adjust, Review) shown at the top of Fig. 4, which guides clinicians in personalized asthma review and adjustment of treatment. This approach emphasizes the principle that asthma treatment is not 'one size fits all'.

Management of each patient's individual risk factors and comorbidities may include both pharmacologic and non-pharmacologic strategies. Non-pharmacologic strategies may include smoking cessation advice, breathing exercises, weight reduction, avoiding air pollution and allergens, appropriate immunizations as well as strategies for dealing with emotional stress. In addition, it is essential to ensure patients can use their prescribed inhaler correctly with reinforcement of approved local videos (e.g., https://www.nationalasthma.org.au/living-with-asthma/how-to-videos). In patients with severe asthma, assessment of inflammatory biomarkers (blood eosinophils and/or FeNO) is important for guiding selection and adjustment of asthma treatment.

A written or pictorial action plan on the management of asthma exacerbations should be provided to every patient. The action plan should be appropriate for the patient's level of literacy and health literacy, and their treatment regimen. Examples of action plans, including for patients using ICS–formoterol reliever as in GINA Track 1, are available at https://www.nationalasthma.org.au/health-professionals/asthma-action-plans/asthma-action-plan-library. The risk of adverse effects of medications can be reduced by optimizing inhaler technique and adherence, stepping down ICS dose when asthma has been well-controlled for 2–3 months, by referring patients for specialist review (if available) if asthma is not well controlled despite medium or high dose ICS-LABA, and by identifying patients with SABA overuse who may be potentially switched to GINA Track 1 with an ICS–formoterol reliever.

Figures 5 and 6 summarize the GINA options for *initial* asthma medications in adults, adolescents and children 6–11 years newly diagnosed with asthma. Once treatment has been initiated, ongoing medication decisions are based on the same personalized cycle, in which treatment is stepped up and down according to the patient's needs within a track, using the same reliever. Treatment can also be switched between tracks according to patient needs and preferences. Before any step-up (Fig. 2), it is essential to check adherence to treatment, inhaled technique, relevant comorbidities and risk factors, and environmental factors affecting asthma (Supplementary Fig. 1).

ASSESSMENT OF ASTHMA CONTROL IN TWO DOMAINS: SYMPTOMS AND RISK FACTORS

GINA defines asthma control in two domains: (i) current symptom control and (ii) risk factors for future poor asthma outcomes

People with asthma should be assessed regularly, including after flare-ups. Unfortunately, in many cases, asthma is managed as

Table 4. Specific questions to ask when assessing children 6–11 years with asthma.

Asthma symptom control	
Day symptoms	Ask: How often does the child have cough, wheeze, dyspnea or heavy breathing (number of times per week or day)? What triggers the symptoms? How are they handled?
Night symptoms	Cough, awakenings, tiredness during the day? (If the only symptom is cough, consider other diagnoses such as rhinitis or gastroesophageal reflux disease).
Reliever use	How often is reliever medication used? (check date on inhaler or last prescription) Distinguish between pre-exercise use (sports) and use for relief of symptoms.
Level of activity	What sports/hobbies/interests does the child have, at school and in their spare time? How does the child's level of activity compare with their peers or siblings? How many days is the child absent from school? Try to get an accurate picture of the child's day from the child without interruption from the parent/carer.
Risk factors for adverse outcomes	
Exacerbations	Ask: How do viral infections affect the child's asthma? Do symptoms interfere with school or sports? How long do the symptoms last? How many episodes have occurred since their last medical review? Any urgent doctor/emergency department visits? Is there a written action plan? Risk factors for exacerbations include a history of exacerbations, poor symptom control, poor adherence and poverty, and persistent bronchodilator reversibility even if the child has few symptoms.
Lung function	Check curves and technique. Main focus is on FEV_1 and FEV_1/FVC ratio. Plot these values as percent predicted to see trends over time.
Side-effects	Check the child's height at least yearly, as poorly controlled asthma can affect growth, and growth velocity may be lower in the first 1–2 years of ICS treatment. Ask about frequency and dose of ICS and OCS.
Treatment factors	
Inhaler technique	Ask the child to show how they use their inhaler. Compare with a device-specific checklist.
Adherence	Is there any controller medication in the home at present? On how many days does the child use their controller in a week (e.g. 0, 2, 4, 7 days)? Is it easier to remember to use it in the morning or evening? Where is inhaler kept – is it in plain view to reduce forgetting? Check date on inhaler.
Goals/concerns	Does the child or their parent/carer have any concerns about their asthma (e.g. fear of medication, side-effects, interference with activity)? What are the child's/parent's/carer's goals for treatment?
Comorbidities	
Allergic rhinitis	Itching, sneezing, nasal obstruction? Can the child breathe through their nose? What medications are being taken for nasal symptoms?
Eczema	Sleep disturbance, topical corticosteroids?
Food allergy	Is the child allergic to any foods? (confirmed food allergy is a risk factor for asthma-related death)
Obesity	Check age-adjusted BMI. Ask about diet and physical activity.
Other investigations (if needed)	
2-week diary	If no clear assessment can be made based on the above questions, ask the child or parent/carer to keep a daily diary of asthma symptoms, reliever use and peak expiratory flow (best of three) for 2 weeks (Appendix Chapter 4).
Exercise challenge (laboratory)	Provides information about airway hyperresponsiveness and fitness (Box 1–2). Only undertake a challenge if it is otherwise difficult to assess asthma control.

Source: Box 2–3 in GINA 2022. Box and appendix numbers refer to GINA 2022 report. Reproduced with permission from ref. [11].
FEV_1 forced expiratory volume over 1 s, *FVC* forced vital capacity, *ICS* inhaled corticosteroid, *OCS* oral corticosteroid.

though it were an acute illness; patients are treated for flare-ups and then sent home without follow-up[42–46].

Patient-reported tools for assessing asthma symptom control (e.g., Asthma Control Questionnaire, Asthma Control Test, Childhood Asthma Control Test) reflect only the past 1–4 weeks, and therefore provide only a snapshot of recent symptoms, not overall asthma control.

Poor symptom control is associated with an increased risk of asthma flare-ups. However, people with good symptom control or seemingly mild asthma can still be at risk of severe flare-ups (severe exacerbations)[47], and even death[48]. GINA therefore recommends that asthma control should be assessed in two domains: (i) current symptom control and (ii) risk factors for future poor asthma outcomes, particularly exacerbations (Supplementary Fig. 1).

Supplementary Fig. 1 summarizes how to assess symptom control and provides a list of modifiable risk factors for exacerbations that are independent of the level of symptom control. This means that even if someone has no current or recent symptoms at the time of assessment, they may still be at risk of asthma flare-ups. Treatment of modifiable risk factors may include, for example, correcting inhaler technique, reducing exposure to tobacco smoke, strategies for weight reduction, allergen immunotherapy and/or allergen avoidance in sensitized patients, and arranging mental health support.

Table 4 summarizes specific questions to be addressed when assessing asthma control in children 6–11 years.

DIFFICULT-TO-TREAT AND SEVERE ASTHMA

Refer people with severe asthma to a respiratory specialist, if possible

Difficult-to-treat asthma is defined as asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller (usually a LABA) or with maintenance oral corticosteroids, or that requires high-dose ICS to maintain good asthma control. For many such patients, their asthma can be well controlled by optimizing care, including identifying and addressing modifiable risk factors listed in Figs. 2 and 7 and Supplementary Fig. 1. Poor adherence and incorrect inhaler

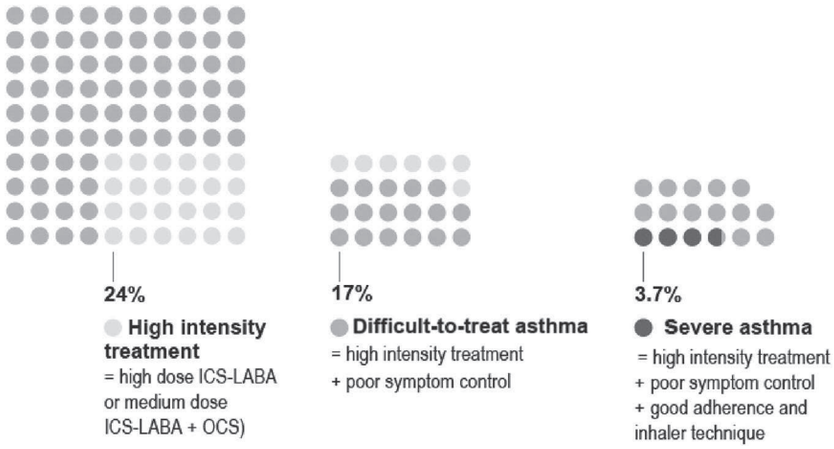

Fig. 8 Proportion of adults with difficult-to-treat or severe asthma. Severe asthma is a subset of those with "difficult-to-treat" asthma. Source: Box 3–15 in GINA report 2022, data from Hekking et al.[49]. Reproduced with permission from ref. [11].

technique are particularly common contributors to poor asthma control.

Severe asthma is a subset of difficult-to-treat asthma (Fig. 8). Severe asthma is defined as asthma that is uncontrolled despite adherence with optimized high-dose ICS-LABA treatment with correct inhaler technique and management of contributory factors such as comorbidities and environment exposures, or that worsens when the dose of ICS-LABA is reduced.

Based on a study in the Netherlands, about 3–4% of people with asthma are estimated to have severe asthma[49], but many more patients have difficult-to-treat asthma, that could be improved by referral for specialist assessment and treatment[50]. While a small proportion of people with asthma have severe disease, they contribute towards a disproportionately high level of morbidity, mortality and healthcare costs[51,52].

While most people with asthma can be managed in primary care, it can be challenging to identify those at risk of poor outcomes, and especially those with severe asthma. This difficulty is partly due to the nature of primary care, where large numbers of patients present with many different and often previously undiagnosed medical conditions, there can be severe time pressures, resources may be limited, and at follow-up a patient may see different healthcare professionals with varying levels of expertise or training about asthma. Furthermore, medical records may be poor or incomplete, making it difficult to form a perspective of long-term control and efficacy of treatments, and specifically correctly identifying those that may benefit from specialist referral.

When asthma is poorly controlled despite medium or high dose ICS-LABA, the patient should be reassessed. This involves first ensuring that the diagnosis of asthma has been confirmed and relevant comorbidities and risk factors managed, that ICS have been prescribed, and that asthma treatment has been optimized; that is, that the patient is collecting and using the medication and that they are satisfied with[53] and are able to use their inhaler correctly[54,55].

Figure 7 shows other factors and interventions that can also be considered in primary care. If asthma remains uncontrolled, there are several reasons why these people should be referred (if possible) for expert assessment, advice and/or provision of medication, and for guidance on ongoing primary care management. In addition to confirming the diagnosis, specialist asthma services have knowledge of, and access to, newer and specific treatment including the latest range of biologic treatments (monoclonal antibodies for severe asthma). They may also have access to specialist nursing, pharmacists, counseling and psychology expertise and the facilities to provide long-term follow-up and access to consistent support from liaison nurses.

While some primary care clinics may have such expertise and resources, most do not. A number of UK coronial inquests on asthma deaths in children concluded that lack of access to continuity of care contributed to these deaths[42–44].

The section of the GINA 2022 report on severe asthma diagnosis and management spans the roles of clinicians ranging from primary to tertiary care. Figure 7 summarizes the initial approach to these patients in a primary care setting. The full severe asthma recommendations (including for biologic therapy) as well as a summary booklet are also available on the GINA website.

While most patients' asthma can be managed in primary care, specialist opinion and treatment is strongly recommended (where available) in some situations:

- when the diagnosis is difficult; specialists will have access to more sophisticated investigations and resources for confirming or excluding a diagnosis of asthma;
- when there is failure to control symptoms despite adequate therapy, good adherence and good inhaler technique;
- when severe asthma is suspected, for characterization of phenotype and for consideration of biologic therapy, depending on availability. For example, primary care physicians should consider referral for patients taking maintenance oral corticosteroids and those who have had two or more courses of oral corticosteroids for acute exacerbations in the previous year, and those who have poorly controlled asthma despite step 4 treatment;
- when symptoms suggest complications or comorbidities such as aspirin-exacerbated respiratory disease, allergic bronchopulmonary aspergillosis;
- when occupational asthma is suspected;
- when a patient has a history of a life-threatening asthma attack, or has confirmed or suspected food allergy as well as asthma.

CONCLUSION

In summary, the GINA strategy emphasizes that asthma should be considered in the differential diagnosis of anyone presenting with respiratory symptoms, particularly if recurrent and varying in severity. Where possible, the diagnosis of asthma should be confirmed with lung function testing before initiating controller treatment. Asthma control should be assessed in two domains: current symptom control and risk factors for future asthma flare-ups (exacerbations), which include having had a flare-up in the

previous 12 months. Asthma treatment for all patients should include ICS: either regularly or (in mild asthma) as needed whenever symptom reliever is taken.

Optimization of asthma treatment includes education and skills training for inhaler technique and adherence, and provision of a written/pictorial asthma action plan. Failure to successfully optimize care in people with severe or difficult-to-treat asthma should prompt careful reassessment—if available, by a specialist with appropriate facilities for diagnosis and interdisciplinary treatment. Collaboration between primary care doctors and respiratory physicians is a key factor in effective asthma management.

DATA AVAILABILITY

No datasets were generated or analyzed during the current study.

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One-minute sit-to-stand test as a quick functional test for people with COPD in general practice

J. G. Spence[1,2,3]✉, J. Brincks[2], A. Løkke[4,5], L. Neustrup[6] and E. B. Østergaard[3]

Assessing changes in functional exercise capacity is highly relevant in the treatment of people with Chronic Obstructive Pulmonary Disease (COPD), as lung function is often static. In Denmark, most people with COPD are followed in general practice where traditional functional tests, like six-minute walk test, require too much time and space. Therefore, there is an urgent need for a quick functional exercise capacity test that can be performed in a limited setting, such as general practice. This study aimed to identify a quick test to measure functional exercise capacity in people with COPD and identify which factors could affect the implementation of such a test in general practice. A mixed method feasibility study composed of a literature review and qualitative interviews was used. Quick functional tests for people with COPD were identified and evaluated through the COSMIN methodology. For the interviews, 64 general practices were included, and 50 staff members and 14 general practitioners (GPs) participated in the interviews. Responses were categorized and thematically analyzed. The 1 min sit-to-stand-test (1 M STST) was found suitable for a general practice setting. The COSMIN methodology rated it "sufficient" in reliability (ICC 0.90–0.99), measurement error (MID 2.5–3), construct validity and responsiveness (AUC 0.72), and found a moderate to strong correlation in criterion validity ($r = 0.4$–0.75). Several GPs wished for a quick functional test and emphasized evidence, information, and limitations as essential when deciding on implementation. Other factors identified included time, other tests, and economy. 1 M STST is a valid test to assess functional exercise capacity in people with COPD. The test is quick and can easily be performed in a standard consultation, and several GPs wished for such a test.

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INTRODUCTION

In Denmark, most people with Chronic Obstructive Pulmonary Disease (COPD) are treated in general practice and assessed at annual check-ups[1,2]. However, despite strong evidence for the positive impact of physical activity and rehabilitation, for people with COPD[3,4], studies have uncovered a significant focus on medication and only a minor focus on physical activity among general practitioners (GPs) in Denmark[5,6].

As a part of pulmonary rehabilitation, healthcare professionals measure improvements in functional exercise capacity[5]. This measurement is essential as people with COPD have a significantly lower activity level than healthy, age-matched individuals[7]. There are many barriers to physical activity, such as lack of motivation, fear of shortness of breath or anxiety[5,8]. Therefore, assessing changes in functional exercise capacity is vital to ensure that people with COPD stay physically active.

Functional exercise capacity can be described as a persons maximal performance in the physical domain[9,10]. If functional exercise capacity decreases, symptoms will likely increase as the functional reserve during everyday activities will diminish. In COPD, reduced functional exercise capacity may lead to increased dyspnea and fatigue, which can trigger anxiety during certain activities and therefore cause inactivity. Exercise and increased physical activity could prevent this vicious circle by improving functional exercise capacity and decreasing symptom burden[3].

The lung function test (spirometry) is often used in general practice to diagnose COPD and to assess the degree of lung function impairment[2], and for this purpose, the test is valid[11]. However, lung function does not correspond to functional exercise capacity[7]. Because of the progressive nature of COPD, lung function will often decrease over time, even if functional exercise capacity improves. This might negatively impact the motivation for continued physical activity and reduce the GP's incentive for positive dialogue about physical activity[6].

The Global strategy of management, diagnosis and prevention of COPD describes important guidelines and mentions functional exercise capacity as one of the important factors in describing disease severity and progression of COPD[11]. The guidelines recommend the 6 min walking test (6MWT) for testing functional exercise capacity at check-ups in general practice[11]. Unfortunately, with limited time and space, traditional tests are difficult to implement in general practice. Therefore, there is an unmet need for a quick and feasible functional exercise capacity test—especially in general practice.

Our study aimed to (1) identifying a quick, valid functional test capable of assessing functional exercise capacity for people with COPD in settings where time and space are limited and (2) exploring factors, through interviews with staff members and GPs, that could affect the implementation of such a test in general practice.

METHODS

A feasibility study with method triangulation was conducted. The study consisted of a literature review and fieldwork interviews with 64 general practices in Denmark in 2021. The feasibility

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design was based on two framing questions: Does it work? Will it work?[12]. The framing questions made up the two phases of our study. They originated from a preconception of general practice to chronologically explore a hypothetical implementation of a quick functional test in general practice. First, a search for systematic reviews involving functional exercise capacity tests for people with COPD was conducted. Second, an assessment of the most suitable functional exercise capacity tests for limited settings was performed using the COSMIN methodology[13]. Qualitative, semi-structured interviews with 64 general practices were performed: 50 staff members (medical secretaries and nurses) were interviewed by telephone and 14 GPs by e-mail. Responses were categorized and thematically analyzed.

Data collection—phase one

The search for literature was conducted within EMBASE, PUBMED and CINAHL. A PICOT - approach was used and focused on systematic reviews concerning functional tests for people with COPD (Supplementary Figure 1). After titles and abstracts were screened, it resulted in five systematic reviews[14–18]. Inclusion and exclusion criteria for the quick functional tests were conceived from the preconceptions of general practice. Functional exercise capacity tests were excluded if specialized equipment or skills unsuitable for GPs or nurses were required, if a space larger than 6×4 meters was required, or if the time required for the test was 5 min or more (including instruction). For inclusion, the test had to be valid to assess functional exercise capacity for people with COPD and comparable with traditional functional tests like the 6MWT and the Shuttle walk test (SWT).

Based on the criteria and literature about functional tests, the 1 min sit-to-stand-test (1 M STST) was found most suitable to measure relevant clinical outcomes in people with COPD[19,20]. A PICO-search was performed within the before-mentioned databases focusing on validity and correlation with functional tests such as 6MWT and the SWT (Supplementary Figure 2). Three articles were found after abstracts were read[19,21,22]. The reference lists for eligible trials were screened for additional relevant articles, and four more were found[20,23–25]. In total, seven articles were included in the COSMIN assessment.

COSMIN assessment

The 1 M STST was assessed using the COSMIN methodology. The COSMIN methodology is a modular tool to review outcome measurement tools systematically. The COSMIN Checklist was chosen as it specifically reviews the measurement tool and its properties by using the articles, instead of evaluating the articles independently. The version of the COSMIN checklist was created for patient-reported outcomes measurements, but it is also recommended for performance-based measurements[13].

The checklist consists of four stages: (1) The measurement properties (Validity, reliability etc.) from the 1 M STST, which were investigated in the included articles, were identified. (2) The included articles' methodological quality was evaluated using the *COSMIN Risk of Bias checklist*. (3) The investigated measurement properties and their outcomes from the included studies were evaluated through the standards of good measurement properties from the *COSMIN criteria for good quality*. (4) The evidence was then summarized, and the quality of the summarized evidence was evaluated with the *GRADE approach* from the COSMIN methodology[13,26].

The results for each measurement property were accumulated and assessed as *sufficient, insufficient, inconsistent* or *indeterminate*. The quality of evidence in each measurement property was evaluated based on studies investigating the measurement property in the following areas: Risk of bias, inconsistency, imprecision and indirectness[13].

Data collection—phase two

Literature and documents about general practice in Denmark were explored on government and general practice relevant websites, focusing on annual check-ups and monitoring, organizational structure and economy in preparation for composing relevant questions for the interview[2,27–29]. Two interview guides were composed, one with a general focus and one with a specific focus (Supplementary Figure 3). The general focus interview addressed staff members performing tests and time allocated for testing and was conducted as telephone interviews with 50 staff members from general practice. The specific focus interview addressed staff, time, tests performed at annual check-ups, and factors regarding implementing a quick functional test for people with COPD and was conducted as e-mail interviews with 14 GPs. Telephone and e-mail interviews were used because of the COVID-19 pandemic during the testing period.

The results were collected and arranged. One of the staff members and two of the GPs, could not answer the question regarding time spent. Furthermore, one GP did not elaborate on the tests for annual check-ups.

In questions where an interviewee had two answers in the same category, e.g., if both nurses and doctors were conducting the tests or more than one test were performed during the consultation, both answers were included. Still, the total number of answers was not increased.

Data analysis

Answers about factors regarding implementing a quick functional test were categorized and thematically analyzed. For the analysis of the empirical data, Malterud's thematic analysis was used[30]. This method was used because it identifies patterns and themes in the answers from the interviewees. The method uses decontextualization and recontextualization in a four-step approach to identify important themes in the qualitative datasets collected in the interviews. The steps were: An overall impression of the answers and themes in the interview, identification of meaningful entities in the answers, condensation of the entities and at last, a synthesis of the identified themes.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

ETHICS

The participants were informed about the aims of the study, the method and professional confidentiality. Based on that, the participants gave informed consent[31].

The data was anonymized, including the names of the participants and the general practices to protect individual confidentiality according to The Declaration of Helsinki[31,32]. According to Danish law, Scientific Ethical Committees Act §14 no. 2, research based on interviews and questionnaires is exempt from ethical approval[33]. Since the study was solely based on interviews, ethical approval was not required by regulatory authorities in Denmark[33].

RESULTS—PHASE ONE

As shown in Table 1, the 1 M STST has an overall rating from the COSMIN checklist of *sufficient* in reliability, measurement error, construct validity and responsiveness. The quality of evidence in these categories is rated high, as the studies included have a sample size above 100, show consistent results in multiple studies, construct validity, and share a similar confirmed hypothesis. The results in criterion validity are *inconsistent* as some of the values

Table 1. COSMIN summary of evidence.

	Results	Overall rating	Quality of evidence
Reliability	ICC[a]-range: 0.902–0.99 Consistent results: yes Sample size range: 42–203	Sufficient	High: Multiple studies showing good effect
Measurement error	MID[b]-range: 2.5–3 Sensitivity 80% Specificity: 60%	Sufficient	High: One study with sample size $n = 50–100+$
Criterion validity	Correlation range: 0.4–0.75 AUC[c]: 0.82	Inconsistent	Moderate: Two out of four studies with correlation under COSMIN limit.
Construct validity	Hypothesis confirmed: 4/4	Sufficient	High: Similar hypothesis in correlation with 6MWT[d], consistent results
Responsiveness	AUC: 0.716 SMD[e]: 0.87–0.91	Sufficient	High: Two studies with consistent results

[a]Intraclass Correlation Coefficient.
[b]Minimal Important Difference.
[c]Area Under Curve.
[d]Six minute walk test.
[e]Standard Mean Deviation.

for correlation are below the criteria for good measurement qualities in the COSMIN methodology ($r \geq 70$ or area under curve ≥0.70). This downgrades the quality of evidence from high to moderate as the results are inconsistent. However, the correlation is still rated as moderate to strong.

RESULTS—PHASE TWO

Results from the general and specific interviews can be seen in Table 2.

From the general interview, it was found that most general practices (85.9%) used nurses or a mix of nurses and other staff members to perform tests at the annual check-up. Medical students were the second largest group to perform the tests in general practices (14%).

In most general practices, the regular amount of time allocated for the annual check-up was 30 min, with 38 practices having this as their fixed amount of time for tests to be performed. Nine practices allocated 15 min, and five allocated 15–30 min depending on the number of tests planned at the check-up.

All practices included in the specific interview ($n = 13$) performed spirometry with or without reversibility. Spirometry with reversibility was only performed at the first meeting in the included general practices. Otherwise, spirometry without reversibility was used. Other tests were blood samples ($n = 6$) and questions about diets, smoking status, alcohol consumption and physical activity level (In Denmark known as KRAM[34]) ($n = 5$).

The thematic analysis identified four themes important for the implementation of a quick functional test such as the 1 M STST: (1) Lack of evidence for a quick functional test, (2) meaningful information about the test is needed, (3) the test is not relevant, and (4) limitations of the test.

All the statements are made by GPs working in General Practices in Denmark. Most GPs (10 of 14) had a positive attitude toward implementing a quick functional test in general practice. One of the GPs replied:

> *"We often need (quick) tests for qualifying the functional status of the patient."*

However, they found it important and central that the test should be experienced as meaningful for people with COPD, and they wanted evidence for the test to be valid to assess functional exercise capacity:

Table 2. Answers from interviews.

Who are testing? ($n = 64$)	Nurses: 55 (85.9%)
	GP[a] secretary: 3 (4.6%)
	Medical students: 9 (14%)
	Care-assistants: 5 (7.8%)
	Practice assistants: 3 (4.6%)
	GP's: 3 (4.6%)
	Medical laboratory Technician: 1 (1.5%)
Amount of time allocated to testing at annual check-ups ($n = 61$)	10 min: 1
	15 min: 9
	20 min: 3
	15–30 min: 5
	25 min: 3
	30 min: 38
	40 min: 1
	45 min: 1
Which tests are performed? ($n = 13$)	Spirometry w/o reversibility: 13
	Electrocardiogram: 4
	Blood samples: 6
	KRAM[b]: 5
	CAT[c]-score: 4
	MRC-scale[d]: 3
	SpO2: 3
	Weight measuring: 3
	GOLD[e]-classification: 2
	Bloodpressure: 2
	Inhalation technique: 2

[a]General Practitioner.
[b]Diet – Smoking - Alcohol-consumption - Physical activity.
[c]COPD Assessment Test.
[d]Medical Research Council – Dyspnea scale.
[e]Severity of COPD.

> *"Yes, we would implement the test, if it was relevant for the patient"*

> *"You could definitely do it [Implement the test (red.)], if there is evidence that it will add something useful regarding the functional exercise capacity"*

Among both sides, the positive toward implementation and the negative toward implementation, there were mentions about limitations regarding the 1 M STST in general practice:

> *"[…] I do have some who wouldn't be able to finish because of decreased general condition"*

> *"As a solo general practitioner, I don't share information in a team and document primarily for my own sake. You make an observation from the waiting room to the office, which you then use for assessing the MRC [MRC Dyspnea Scale (red.)]"*

One GP considered the 1 M STST not challenging enough for younger people with COPD and maybe too challenging for older people with COPD and decreased general condition. Another GP considered general observations for Medical Research Center Dyspnea scales (MRC-scale) or 30 s sit-to-stand test (30STST) sufficient for assessing functional exercise capacity. A third GP stated that some general practices solely implement tests recommended by their professional association.

DISCUSSION

1 M STST is assessed as *sufficient* for the measurement qualities; reliability, measurement error, construct validity and responsiveness. The quality of evidence is assessed high for the same measurement qualities.

Criterion validity is assessed as *inconsistent* with moderate quality of evidence, as two out of four studies had correlation values below the limit for good measurement qualities according to COSMIN ($r \geq 0.7$)[13]. However, the correlation $r = 0.4–0.75$ in the studies is still moderate to strong[19–21,23]. Studies assessing criterion validity, e.g., validity compared to the 6MWT, underline that the 1 M STST is comparable with the 6MWT[21–24]. However, it is relevant to point out that the 6MWT and the 1 M STST assess functional exercise capacity in two different relevant functions of daily life, walking and sit-to-stand. Therefore, they can never be fully comparable.

Several studies in the COSMIN assessment did not include people in a weakened state or with musculoskeletal problems[19,21,24,35]. Therefore, these people must be assessed individually, which GPs also pointed out in the interviews as a limitation of the test.

The possible implementation of a quick functional test in general practice and some ways to comply with challenges on this matter were analyzed. A large variation in general practises was found, which underlines the importance of cooperating with the specific general practice to uncover the specific factors regarding an implementation. To determine factors influencing the implementation process, specific focus areas were explored from the feasibility concept[12]: practicality, expansion and demand.

The 1 M STST is considered practical as the only remedies required for carrying out the 1 M STST are a chair and a stopwatch (Supplementary Figure 4). The test protocol is accessible and easy to perform, even considering the registered diversity among the staff members performing tests in general practice[36] (Table 2). In regards to expansion the study found that general practice has an average time allotted for annual check-ups of 30 min. The lung function test, used by all interviewed GP's, varies in time, whether acceptable results are obtained quickly, but requires ~10 min to be performed[37]. The GPs interviewed defined the test battery used for annual check-ups in general practice as a modulated toolbox, adjustable and dependent on the person's needs, more than a rigidly defined test battery. If so, it is reasonable to believe that the 1 M STST can be implemented. The results of this study show that the 1 M STST should be included in the test battery based on its relevance to people with COPD.

The general practices in Denmark receive a fixed annual fee per person with COPD[27–29]. This means that implementation will not alter the economic frame as it is fixed annually. In other countries, other financial systems might be in place, but the 1 M STST should be implementable based on its relevance to the person and its accessibility and low requirement for time and space.

Several of the interviewed GPs asked for a quick functional test, and the requested evidence has been determined in this study through the COSMIN methodology. In making test results more tangible and usable for the people and the GP, reference values will be appropriate. For example, a study from 2013 by Strassmann et al. with 6.926 healthy adults gave insight into average values for healthy individuals classified in age and gender[38]. These reference values and the minimal important difference (MID) of three repetitions for the 1 M STST, will be relevant and useful information for the person and the GP when implementing the test in general practice[25].

The 1 M STST complies with all inclusion and exclusion criteria from the initial literature search. It was found that the 1 M STST is valid compared to the 6MWT, and the test results correlate with the quality of life and 2-year mortality[23,24,35,39].

In general practice, the MRC-scale assesses the need for pulmonary rehabilitation or intensified focus on physical activity[2]. One of the interviewed GPs used it for categorizing functional exercise capacity. The MRC-scale is self-reported, and in 2014 Callens et al. found that one in four people with cardio-respiratory disorders over-or underestimated their actual functional exercise capacity on recall, especially people diagnosed with COPD[40]. Therefore, the MRC-scale is problematic when it comes to identifying the need for intervention regarding physical activity, and the 1 M STST can provide a more objective measure of functional exercise capacity for the GP. Neither the MRC-scale nor the 30STST assess functional exercise capacity in people with COPD as the 1 M STST[19,20].

The articles found in our present study also conclude that the 1 M STST has high test-retest reliability (ICC 0.99 (95% CI 0.97–1)) and low learning effect (ICC 0.93 (95% CI 0.83–0.97)), which means that it only needs to be tested once to get a reliable result[20,22]. This underlines the relevance of the 1 M STST when assessing functional exercise capacity in time-limited settings. The 1 M STST responds to changes in functional exercise capacity and has a MID of three repetitions[22,25]. These results on the 1 M STST are supported in an extensive systematic review from 2019, where the 1 M STST is recommended, especially in settings where time and space are limited[36]. A recent study from 2022 also found that having a follow-up using the 1 M STST also had a clinically relevant benefit on functional status in people with COPD[41].

The method triangulation in this study has strengthened the feasibility concept by exploring the research aims in different ways from different perspectives. The process of this project was evaluated continuously with the four quality criteria in qualitative projects[42]. The COSMIN methodology findings in this study are comparable to earlier studies, strengthening the external validity[14,15].

The in- and exclusion criteria for the literature search were created to find a quick functional test accessible to all varieties of general practice settings. As they were based on a preconception, the 1 M STST was performed on GPs and other staff members of general practice at a symposium on COPD to examine if it was feasible in general practices. Based on this feed-back, it was concluded that the criteria for the literature research were sufficient to identify a possible, feasible test.

This article explored only objective focus areas from the feasibility concept (Practicality, expansion, demand). Another important focus area, "Acceptability", about how the patient and the one performing the test experience the 1 M STST, has not been investigated in this study[12]. None of the included studies have mentioned this either. In an implementation of the 1 M STST

into General Practice, the subjective experience of the patient is of paramount importance and should be investigated further in future studies. Most of the interviews were done in one region of Denmark. The e-mail interviews were done with GPs from different areas of Denmark. The similarities in the results justify a generalization of our results to general practices. The variety of staff included and the accessibility of the 1 M STST, compared with the similarities in our results, justifies a generalization of the findings to most general practice.

A possible consequence of the firm structure in the 14 e-mail interviews with the GPs might be that the area regarding factors for implementing a quick functional test has not been fully explored. Focus group interviews could have given a more in-depth view of the barriers and needs in an implementation process. Still, it is believed that this study uncovers variation among general practices concerning attitude towards the test and practicalities.

The results are limited to knowledge about annual check-ups in general practice usable for future research and feasibility studies in this area. Although based on the Danish healthcare system, the results of this study may apply to other healthcare systems internationally, especially regarding the validity and practicality of the 1 M STST and the need for a quick functional exercise capacity test in general practice.

In conclusion, according to COSMIN criteria, the 1 M STST is a valid, reliable, and responsive test to assess functional exercise capacity for people with COPD in general practice. Despite great variation in general practice, the 1 M STST is suitable for implementation because it requires a minimum of time and space for implementation, gives valuable information regarding functional exercise capacity and has therapeutic relevance for people with COPD, especially in general practice.

The results from this study indicate a need among GPs for a quick functional test for people with COPD. The GPs requested that the 1 M STST was valid for assessing functional exercise capacity and that the test was experienced as meaningful for people with COPD. In addition, the 1 M STST works well for factors such as time for consultations, other tests, and economy, which are important in the implementation of a quick functional exercise capacity test.

DATA AVAILABILITY

Anonymised data that support the findings of this study will be made available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

J.G.S., J.B., A.L., and E.B.Ø. contributed with designing the study, J.G.S. and E.B.Ø. performed the preliminary research. The recruitment was performed by J.G.S. with help from A.L. and E.B.Ø. Data collection and analysis was carried out by J.G.S. supervised by E.B.Ø. and J.B. J.G.S. drafted the original paper and revision was performed by all authors of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Ryaltris™ er indisert til voksne og barn over 12 år til behandling av moderate til alvorlige nesesymptomer i forbindelse med allergisk rhinitt.

Dosering
Ryaltris™ er kun til bruk i nesen, den vanlige anbefalte dosen er to sprayer i hvert nesebor to ganger daglig (morgen og kveld).

Utvalgt sikkerhetsinformasjon
Bivirkninger: Vanlige (≥1/100 til <1/10) er dysgeusi, epistakse og ubehag i nesen. **Kontraindikasjon**: Ryaltris™ skal ikke brukes ved ubehandlet, lokal infeksjon i neseslimhinnen, som herpes simplex eller hos pasienter ved nylig gjennomgått nesekirurgi eller traumer før skaden er tilhelet.

Pakninger og priser
1 flaske à 30 ml med 29 g suspensjon (240 spraydoser) kr 223,50

Refusjon
Symptomlindring ved moderat til alvorlig sesongrelatert og helårlig allergisk rhinitt hvis monoterapi med enten intranasalt antihistamin eller glukokortikoid ikke er vurdert som tilstrekkelig.
Refusjonskode: ICPC: R97 Allergisk rhinitt. ICD: J30 Vasomotorisk og allergisk rhinitt. Vilkår: Ingen spesifisert.

Basert på SPC godkjent av SLV/EMA: 20.12.2021
For fullstendig preparatomtale (SPC), se www.legemiddelsok.no

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Predictive and prognostic value of leptin status in asthma

Juan Wang[1,3], Ruochen Zhu[2,3], Wenjing Shi[1] and Song Mao[1]✉

Asthma is closely associated with inflammation. We evaluated the predictive and prognostic value of leptin status in asthma. We searched the electronic databases for articles that determined the leptin level in asthma cases through May 2020. We compared the differences of leptin level between asthma and non-asthma controls, as well as between severe and mild asthma cases. We also investigated the impact of age and gender on these differences by using meta-regression analysis. 59 studies were included in our pooled analysis. Asthma cases demonstrated significantly higher leptin level than that in non-asthma controls among overall populations (SMD:1.061, 95% CI: 0.784–1.338, $p < 10^{-4}$), Caucasians (SMD:0.287, 95% CI: 0.125–0.448, $p = 0.001$), Asians (SMD:1.500, 95% CI: 1.064–1.936, $p < 10^{-4}$) and Africans (SMD: 8.386, 95% CI: 6.519–10.253, $p < 10^{-4}$). Severe asthma cases showed markedly higher leptin level than that in mild asthma cases among overall populations (SMD:1.638, 95% CI: 0.952–2.323, $p < 10^{-4}$) and Asians (SMD:2.600, 95% CI: 1.854–3.345, $p < 10^{-4}$). No significant difference of leptin level between severe and mild asthma was observed in Caucasians (SMD:−0.819, 95% CI: −1.998–0.360, $p = 0.173$). Cumulative analyses yielded similar results regarding the difference of leptin status between asthma and non-asthma controls, as well as between severe and mild asthma cases among overall populations. Age and male/ female ratio were not associated with the difference of leptin status between asthma and non-asthma controls (coefficient:−0.031, 95% CI: −0.123–0.061, $p = 0.495$; coefficient:0.172, 95% CI: −2.445–2.789, $p = 0.895$), as well as between severe and mild asthma cases among overall populations (coefficient:−0.072, 95% CI: −0.208–0.063, $p = 0.279$; coefficient: 2.373, 95% CI: −0.414–5.161, $p = 0.090$). Asthma demonstrated significantly higher level of leptin than that in non-asthma controls among overall populations, Caucasians, Asians and Africans. Severe asthma cases showed markedly higher leptin level than that in mild cases among overall populations and Asians. Leptin may be a risk predictor and prognostic marker of asthma. Early monitoring and intervention of leptin may be needed for asthma.

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INTRODUCTION

Asthma, a common respiratory tract disease, is likely to occur in both children and adults[1]. Frequent attacks of asthma may lead to irreversible airway obstruction, cardiac events, and even death[2]. In terms of the morbidity and mortality of asthma, early prevention and monitoring of asthma seems imperative. The past decades witnessed an increasing trend of asthma prevalence across the world due to many factors, such as environmental and lifestyle changes[3]. Allergy and inflammation are well-documented inducers of asthma, whereas the occurrence and progression of certain asthma cases remained unexplained[4]. Hence, an in-depth investigation of the potential risk factors for asthma susceptibility and progression is necessary.

Leptin, a hormone secreted by adipocyte, plays a main role in controlling body weight through influencing appetite and energy expenditure[5]. Obesity cases demonstrated higher level of leptin than that in normal controls, indicating that obesity may be a leptin resistance condition[6]. Meanwhile, obesity is closely associated with asthma susceptibility[7]. On the other hand, leptin plays a role in the pro-inflammatory activities, which is closely associated with asthma risk and progression[8]. Leptin secretion is associated with bronchial hyperresponsiveness and insulin resistance[9]. Leptin receptor is also expressed in the lung[10]. In this sense, we speculated that leptin may also be associated with asthma risk and progression.

In the past decades, many studies were performed to determine the leptin levels in asthma cases[11–69]. The results were not consistent among the studies. Some investigations yielded that leptin status was significantly higher in asthma cases than that in non-asthma controls, whereas some studies showed a null difference of leptin levels between asthma and controls. An improved understanding of this issue has important significance that early monitoring or intervention may lower the risk or progression of asthma. A previous pooled analysis showed that higher level of leptin was associated with asthma[70]. However, the association between leptin status and asthma progression was not studied.

With the accumulating evidence, we conducted this updated pooled analysis to investigate the predictive and prognostic value of leptin status in asthma, we also studied the influence of age, gender and ethnicities on the differences of leptin status among different groups with the aim of yielding a more robust finding on this issue.

METHODS

Search strategy

We searched the papers that tested the leptin levels in asthma cases through May 2020 by using PubMed, Embase, Cochrane and Chinese WanFang databases. No restriction was imposed on the searched language. The used terms were as follows: (1) leptin, adipocyte, adiponectin; and (2) asthma, bronchial asthma, respiratory tract disease. We searched the associated papers by combining these terms. We also reviewed the references of

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extracted papers. If the same participants were recruited in more than one study, we chose the study with the complete analysis. The participants data were extracted from the public publications, hence the consent was waived. Ethics approval: This study was approved by the institutional review board of Shanghai Sixth People's Hospital (No: 2018–106).

Inclusion and exclusion criteria

Inclusion criteria: (1) case-control, cohort, prospective or observational study; and (2) asthma as the cases; and (3) leptin status (mean and standard deviation or data to calculate them) available.

Exclusion criteria: (1) case reports, reviews and editorials; (2) levels of other factors in asthma; and (3) detailed leptin level was not available and multiple publications of the same data.

Data extraction and synthesis

We extracted the characteristics from each recruited study. The data were recorded as the following: first author's family name, publication year, ethnicity of participants, study design, gender, number of asthma cases and controls, leptin levels, and adjustment for covariates. The criteria for the definition of severe and mild asthma was not totally same among the recruited studies. Severe asthma was defined as the continuous use of inhaled steroids and bronchodilators, and mild asthma as the intermittent use of inhaled steroids or bronchodilators in the majority of enrolled studies. On the other hand, controlled and uncontrolled asthma were defined as severe and mild asthma, respectively. In a word, the severity of asthma depends on the treatment response and dependence across the included studies. We also evaluated the quality of each recruited study using Newcastle-Ottawa Quality Assessment Scale, which included the assessment for participants selection, exposure and comparability. A study can be awarded a maximum of one score for each numbered item within the selection and exposure categories. A maximum of two scores can be given for comparability[71]. Two authors conducted the literature search independently, study selection, quality assessment and data extraction with any disagreements resolved by discussion.

Statistical analysis

Standard mean difference (SMD) was used to measure the differences of leptin levels between asthma and non-asthma controls, as well as severe and mild asthma cases across the recruited studies. Heterogeneity of SMDs across the studies was tested by using the Q statistic (significance level at $p < 0.05$). The I^2 statistic, a quantitative measure of inconsistency across studies, was also calculated. The combined SMDs were calculated using a fixed-effects model, or, in the presence of heterogeneity, random-effects model. In addition, 95% confidence intervals (CIs) were also calculated. We evaluated the influence of a single study on the pooled SMDs by excluding one study in each turn. Subgroup analyses were conducted according to the ethnicity. Meta-regression analyses were performed to investigate the influence of age and gender on the SMDs between asthma and controls, and as well as between severe and mild asthma. Potential publication bias was assessed by Egger's test and Begg rank correlation test at the $p < 0.05$ level of significance. All analyses were performed using STATA version 12.0 (Stata Corp, College Station, TX). $P < 0.05$ was considered statistically significant, except where otherwise specified.

RESULTS

Literature search

We initially extracted 417 relevant publications from the PubMed, Embase, Cochrane and Chinese WanFang databases. Of these, 358 studies were excluded according to the inclusion and exclusion criteria, 59 articles[11–69] were included in our final meta-analysis (Fig. 1). The retrieved data were recorded as follows: first author's surname, publication year, ethnicity, study design, gender (male/female ratio), age, the number of severe asthma, mild asthma, and non-asthma controls. A flow chart showing the study selection is presented in Fig. 1.

Characteristics for included studies

51 studies were identified for the analysis of the differences of leptin levels between asthma and non-asthma controls. 25 studies were performed for the analysis of the differences of leptin levels between severe and mild asthma. These studies were published between 2004 and 2019. Twenty-one studies were conducted in Caucasians, thirty-seven in Asians, and one in Africans. Forty-nine studies were case-control design, six for cross-sectional design, and four for cohort. A total of 1044 severe asthma, 2536 mild asthma and 7176 non-asthma controls. The number of awarded scores of included studies ranged from 4 to 6. Thirty-one studies were awarded for four scores, twenty-five for five scores and three for six scores. As shown in Table 1.

Differences of leptin levels between asthma and controls

Asthma cases demonstrated significantly higher leptin level than that in non-asthma controls among overall populations (SMD: 1.061, 95% CI: 0.784–1.338, $p < 10^{-4}$), Caucasians (SMD: 0.287, 95% CI: 0.125–0.448, $p = 0.001$), Asians (SMD: 1.500, 95% CI: 1.064–1.936, $p < 10^{-4}$) and Africans (SMD: 8.386, 95% CI: 6.519–10.253, $p < 10^{-4}$) (Table 2, Fig. 2). Significant heterogeneity was observed using Q and I^2 statistic for overall populations ($p < 10^{-4}$, $I^2 = 94.1\%$), Caucasians ($p = 0.005$, $I^2 = 54.7\%$) and Asians ($p < 10^{-4}$, $I^2 = 95.2\%$). Exclusion of any single study did not change the overall SMDs for overall populations (95% CI: 0.727–1.455), Caucasians (95% CI: 0.085–0.502) and Asians (95% CI: 0.829–2.014) (Table 2). Cumulative analysis indicated that leptin status was significantly higher in asthma cases than that in non-asthma controls among overall populations (Fig. 3).

Differences of leptin levels between severe asthma and mild asthma

Severe asthma cases showed markedly high leptin level than that in mild asthma cases among overall populations (SMD: 1.638, 95% CI: 0.952–2.323, $p < 10^{-4}$) and Asians (SMD: 2.600, 95% CI: 1.854–3.345, $p < 10^{-4}$) (Table 2, Fig. 4). No significant difference of leptin level between severe and mild asthma was observed in Caucasians (SMD: −0.819, 95% CI: −1.998–0.360, $p = 0.173$) (Table 2, Fig. 4). Significant heterogeneity was observed using Q and I^2 statistic for overall populations ($p < 10^{-4}$, $I^2 = 96.7\%$), Caucasians ($p < 10^{-4}$, $I^2 = 96.5\%$) and Asians ($p < 10^{-4}$, $I^2 = 95.7\%$). Exclusion of any single study did not change the overall SMDs for overall populations (95% CI: 0.682–2.568), Caucasians (95% CI: −2.572–0.692) and Asians (95% CI: 1.548–3.528) (Table 2). Cumulative analysis indicated that leptin status was significantly higher in severe asthma cases than that in mild asthma cases among overall populations (Fig. 5).

Meta-regression analysis of the age/gender in the association between leptin status and asthma risk/progression

Age and male/female ratio were not associated with the differences of leptin status between asthma and non-asthma controls among overall populations (coefficient: −0.031, 95% CI: −0.123 to 0.061, $p = 0.495$; coefficient: 0.172, 95% CI: −2.445 to 2.789, $p = 0.895$) (Table 3). Age and male/female ratio were not associated with the differences of leptin status between severe and mild asthma cases among overall populations (coefficient:

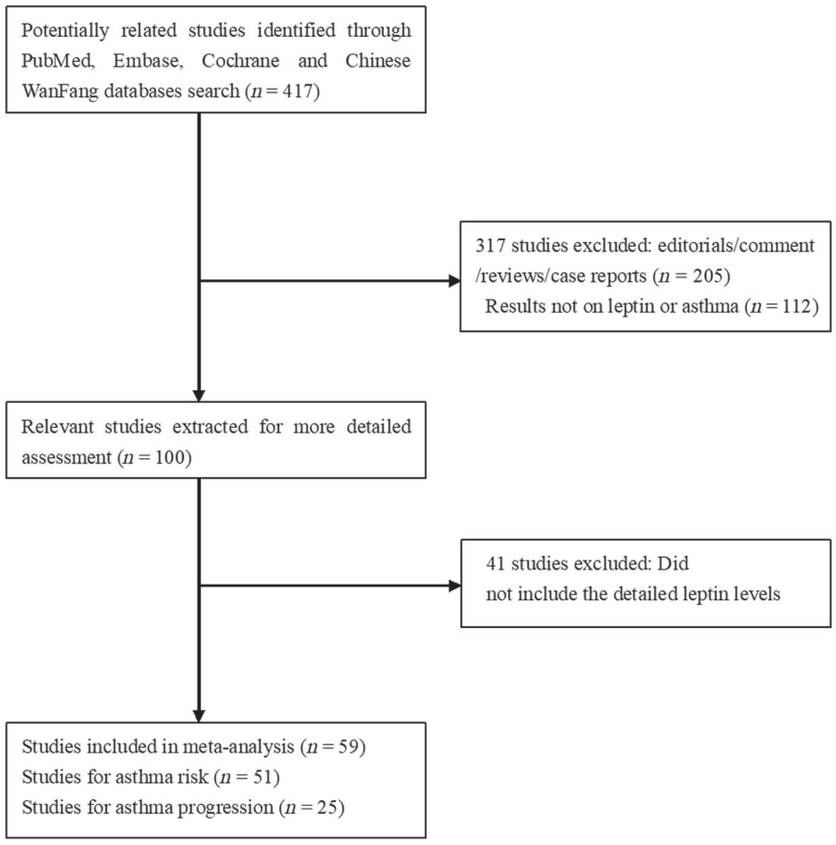

Fig. 1 Flow chart of study selection.

−0.072, 95% CI: −0.208 to 0.063, $p = 0.279$; coefficient: 2.373, 95% CI: −0.414 to 5.161, $p = 0.090$) (Table 3).

Publication bias

The Begg rank correlation test and Egger linear regression test indicated no significant publication bias among Caucasians in the difference of leptin status between asthma and non-asthma controls (Begg, $p = 0.65$; Egger, $p = 0.994$). The Begg rank correlation test and Egger linear regression test showed marked publication bias among Asians in the difference of leptin status between asthma and non-asthma controls (Begg, $p < 10^{-4}$; Egger, $p < 10^{-4}$). The Begg rank correlation test and Egger linear regression test indicated no marked publication bias among Caucasians in the difference of leptin status between severe and mild asthma cases (Begg, $p = 0.230$; Egger, $p = 0.054$). The Begg rank correlation test and Egger linear regression test showed marked publication bias among Asians in the difference of leptin status between severe and mild asthma cases (Begg, $p = 0.002$; Egger, $p = 0.003$).

DISCUSSION

Increasing attention has been paid to the potential role of leptin in the development and progression of asthma. Our pooled analysis showed that asthma cases had markedly higher leptin level than that in non-asthma controls among overall populations, Caucasians, Asians and Africans, and severe asthma cases had significantly higher leptin level than that in mild asthma cases among overall populations and Asians. Age and gender did not influence the association between leptin level and asthma risk/progression. Our results indicated that leptin dysregulation may be associated with asthma risk/progression, frequent monitoring and early intervention of leptin status may be helpful for asthma prevention and therapy.

Several mechanisms may explain the association between leptin status and asthma risk/progression. First, asthma was essentially the breathing problems induced by airway narrowing and obstruction, which was exacerbated by the inflammation[72]. Inflammation was positively associated with the severity of asthma. Systemic inflammation acted as a mechanism linking insulin resistance with asthma[73]. Leptin showed pro-inflammatory actions, stimulating the production of inflammatory cytokines in bronchial and alveolar cells[74]. Persistent stimulation of inflammation may induce the injury and fibrosis of airway, increasing the susceptibility and progress of asthma. Meanwhile, leptin played a role in the regulation of T cell proliferation and activation, monocytes/macrophages recruitment, exerting effects in airway inflammation, respiratory diseases and immune system[75]. In this sense, leptin increased the inflammatory response through various ways, leptin may increase the risk and severity of asthma through activating the inflammation. Second, obesity was a risk factor for asthma susceptibility, and some immune changes present in asthma cases were augmented in obese asthmatics[76]. Meanwhile, obesity was closely associated with an obstructive pattern induced by disproportionated growth between lung parenchyma size and airway caliber, which led to a reduced lung function. Weight loss may lead to an improvement in lung function, airway reactivity and asthma control. Leptin, an adipocyte-derived hormone produced by white fat tissue in the conditions of excessive caloric intake, played a role in controlling body weight by influencing appetite and energy expenditure[77]. Leptin level was higher in obese than that in the normal weight cases, which means that obesity may be a leptin resistance condition. In terms of the close relationship between leptin and obesity, it was reasonable to

Table 1. Characteristics of studies included in our analysis.

Study	Study design	Ethnicity	Case1/Case2/Control				Adjustment for confounding factors	Method Quality of testing score	
			Age(Y)	*n*	male/ female	Leptin			
Doniec et al. [2004][45]	CC	Caucasians	–	–/ 27/ 16	–	–/ 2.84 ± 2.1/ 3.49 ± 1.65 ng/mL	Age	RIA	4
Gurkan et al. [2004][67]	CC	Asians	–/ 6.4 ± 3.1/ 7.0 ± 2.7	–/ 23/ 20	–/ 16/7/ 13/7	–/ 19.3 ± 5.1/ 9.8 ± 1.6 ng/ml	Age, Gender	EIA	5
Guler et al. [2004][64]	CC	Asians	– 5.99 ± 3.46/ 6.12 ± 3.49	–/ 102/ 33	–/ 65/37/ 19/14	–/ 3.53(2.06–7.24)/ 2.26(1.26–4.71) ng/mL median(IQR)	Age, BMI	ELISA	5
Sood et al. [2006][33]	CS	Caucasians	–/ 43.6 ± 1.2/ 44.4 ± 0.7	–/ 290/ 5586	–/ 116/174/ 2709/ 2877	–/ 13.7 ± 0.9/ 11.1 ± 11.2 ug/L	–	RIA	4
Erel et al. [2007][63]	PC	Asians	–	–/ 10/ 33	–	–/ 10.45 ± 11.613/ 7.90 ± 10.609 ng/mL	–	ELISA	4
Kim et al. [2008][68]	CC	Asians	–/ 10.1(8.8–11.5/ 9.1(8.0–11.1) Median(IQR)	–/ 149/ 54	–/ 98/51/ 28/26	–/ 2.27(0.65–5.03)/ 2.10(0.71–4.49) ng/ml median(IQR)	Age, Gender,BMI	ELISA	5
Canoz et al. [2008][66]	CC	Asians	–/ 34.92 ± 10.28/ 33.25 ± 9.50	–/ 24/ 20	Female	–/ 24.38 ± 5.63/ 9.75 ± 1.59 pg/ml	–	IM	4
Chen et al. [2009][61]	CC	Asians	–	–/ 18/ 10	–	–/ 6.82 ± 1.16/ 5.38 ± 1.20 ng/mL	–	RIA	4
Bruno et al. [2009][62]	CC	Caucasians	53(44–61) 46(30–51)/ 29.5(25–34) Median (IQR)	15/ 8/ 15	9/6 / 3/5/ 9/6	2372(867–3714)/ 5722(3547–6761)/ 5300(4031–7514) cells/mm^2 median(IQR)	–	microscope	4
Jang et al. [2009][55]	CC	Asians	– 46.4(18–71)/ 46.4(19–70)	–/ 60/ 30	– / 16/44/ 8/22	–/ 2.31 ± 0.04/ 2.22 ± 0.06 ng/mL	Age, Gender, BMI	ELISA	5
Xiao et al. [2009][20]	CC	Asians	7.2 ± 2.2/ 6.9 ± 2.3/ 7.5 ± 3.1	20/ 18/ 20	11/9/ 10/8/ 8/12	3.62 ± 0.17/ 3.04 ± 0.11/ 2.26 ± 0.12 ug/L	–	ELISA	4
Arshi et al. [2010][60]	CC	Caucasians	– 11.6 ± 3.1/ 11.8 ± 3.3	–/ 21/ 10	–	–/ 9.7 ± 12.4/ 7.1 ± 6.0 ng/mL	Age, Gender, BMI	ELISA	5
Quek et al. [2010][58]	CC	Asians	– 8.74 ± 2.73/ 8.16 ± 1.86	–/ 68/ 46	–/ 38/30/ 29/17	–/ 12.59 ± 12.22/ 8.73 ± 8.04 ng/mL	Age	ELISA	5
Pan et al. [2011][23]	CC	Asians	18–68/ 18–68/ 25–66	70/ 70/ 60	36/34/ 36/34/ 32/28	8.64 ± 0.75/ 2.77 ± 0.02/ 2.32 ± 0.01 ng/mL	Age, Gender, Height, Weight	RIA	4
Baek et al. [2011][28]	CC	Asians	–/ 8.0(6.9–9.3)/ 9.0(8.1–10.0)	–/ 23/ 20	–/ 16/7/ 11/9	–/ 4.51 ± 2.61/ 4.81 ± 3.64 ng/mL	Age, Gender	ELISA	5
Dajani et al. [2011][54]	CC	Asians	–	–/ 10/ 12	Female	–/ 831.21 ± 118.71/ 592.54 ± 64.22 signal intensity	–	ELISA	4

Table 1 continued

Study	Study design	Ethnicity	Case1/Case2/Control				Adjustment for confounding factors	Method Quality of testing score	
			Age(Y)	*n*	male/ female	Leptin			
Leivo-Korpela et al. [2011][56]	CC	Caucasians	– 33.9 ± 2.1/ 33.8 ± 2.1	–/ 35/ 32	–	–/ 0.5(0.5–1.1)/ 0.6(0.4–0.8) ng/L median (IQR)	Age, Gender	ELISA	5
Holguin et al. [2011][57]	CC	Caucasians	– 28(18–60)/ 30(22–39) median (range)	–/ 5/ 7	– / 2/3/ 4/3	–/ 2(0.6–11)/ 11(4–17) ng/L median (IQR)	–	ELISA	4
Giouleka et al. [2011][59]	CC	Caucasians	– 52 ± 14/ 50 ± 16	–/ 100/ 60	– / 40/60/ 25/35	–/ 9.6(7.6, 16.25)/ 7.2(4.6, 10.3) ng/mL median(IQR)	Age, BMI	ELISA	5
Tanju et al. [2011][65]	CC	Asians	6.13 ± 3.01/ 5.93 ± 3/ –	16/ 20/ –	8/8/ 11/9/ –	7.75 ± 1.55/ 1.70 ± 1.10/-	Age, Gender, BMI	ELISA	5
Zhang et al. [2012][13]	CC	Asians	5.58 ± 2.34/ 5.58 ± 2.34/ 5.49 ± 2.14	52/ 52/ 43	32/20/ 32/20/ 28/15	13.33 ± 2.53/ 7.92 ± 1.12/ 3.96 ± 2.02 ng/ml	–	RIA	4
He et al. [2012][27]	CC	Asians	51.9 ± 13.68/ 41.35 ± 13.70/ 46.30 ± 11.42	20/ 17/ 20	7/13/ 7/10/ 10/10	33.8 ± 24.02/ 18.93 ± 17.68/ 10.16 ± 6.08 ng/mL	–	ELISA	4
Berthon et al. [2012][50]	CS	Caucasians	–/ –/ –	56/ 41/ 52	–/ –/ –	5050(2689, 8088)/ 3539(2246, 8088)/ 1025(419, 1817)pg/mL median (IQR)	Age, Gender	IA	5
Sideleva et al. [2012][51]	Cohort	Caucasians	–/ 48 ± 6.7/ 43 ± 7	–/ 11/ 15	Female	–/ 19.2 ± 12.1/ 13.7 ± 10.0 gene expression	–	–	4
Rand Sutherland et al. [2012][52]	CC	Caucasians	10.0 ± 10.8/ 16.1 ± 13.9/ –	30/ 54/ –	5/25 / 13/41/ –	23.1 ± 0.9/ 29.3 ± 0.8/ – ng/mL	–	ELISA	4
Yuskel et al. [2012][53]	CC	Asians	– 10.4 ± 2.7/ 10.7 ± 2.9	–/ 51/ 20	– / 29/22/ 9/11	–/ 5.3 ± 6.8/ 2.1 ± 2.4 ng/mL	–	ELISA	4
da Silva et al. [2012][69]	CS	Caucasians	–	–/ 26/ 50	–/ 7/19/ 18/32				
Zhu et al. [2013][11]	CC	Asians	–/ 46.5 ± 6.3/ 44.8 ± 4.6	–/ 20/ 20	–/ 12/8/ 14/6	–/ 8.99 ± 0.79/ 8.43 ± 0.72 ng/ml	Age, Gender	ELISA	6
Zhang et al. [2013][22]	CC	Asians	2.03 ± 0.70/ 54.5 ± 15.3/ 2.22 ± 0.20	53/ 53/ 42	34/19/ 34/19/ 28/14	13.19 ± 3.85/ 6.51 ± 2.24/ 3.96 ± 2.02 ng/mL	–	RIA	4
Tsaroucha et al. [2013][49]	CC	Caucasians	55.3 ± 9.9/ 59.6 ± 7.8/ 57.6 ± 10.9	15/ 17/ 22	Female	31.1 ± 15.5/ 19.2 ± 12.1/ 13.7 ± 10.0 ng/mL	Age, BMI	RIA	5
Abdul Wahab et al. [2013][41]	PC	Asians	12.5 ± 1.4/ 10.75 ± 1.9/ –	4/ 32/ –	2/2/ 22/10/ –	22.25 ± 12.4/ 17.01 ± 14.0/ –ng/mL	Age, Gender, BMI	ELISA	6
Mohammed Youssef et al. [2013][42]	CC	Africans	–/ 10.4 ± 1.3/ 5.5 ± 1.8	–/ 25/ 20	–/ 14/11/ 9/11	–/ 31.3 ± 2.8/ 12.1 ± 1.4 ng/mL	–	ELISA	4
El-Kader et al. [2013][43]	CC	Asians	13.16 ± 3.54/ 13.16 ± 3.54/ –	40/ 40/ –	–/ –/ –	31.43 ± 5.47/ 26.98 ± 4.50/ – ng/mL	–	ELISA	4

Table 1 continued

Study	Study design	Ethnicity	Case1/Case2/Control				Adjustment for confounding factors	Method Quality of testing score	
			Age(Y)	*n*	male/ female	Leptin			
Cobanoglu et al. [2013][44]	CS	Asians	–/ 8.2 ± 1.2/ 8.8 ± 1.4	–/ 23/ 51	–/ 14/9/ 20/31	–/ 5.3(0.4, 27.4)/ 8.8(0.3,31.3) ng/mL median (min, max)	Age, Gender, BMI	EIA	5
Baek et al. [2013][9]	CC	Asians	–/ 8.3 ± 1.6/ 7.8 ± 1.8	–/ 25/ 21	–/ 17/8/ 9/12	–/ 3.3(2.3, 6.3)/ 4.0(1.9,5.7) ng/mL median(IQR)	–	ELISA	4
Liu et al. [2013][46]	CC	Asians	–	–/ M 53/ 56 –/ F 47/ 52	–	–/ 4.51 ± 1.75/ 4.29 ± 1.76 –/ 14.61 ± 2.95/ 13.26 ± 3.66 ug/L	–	ELISA	4
Peng et al. [2014][14]	CC	Asians	10.46 ± 1.93/ 10.46 ± 1.93/ 9.75 ± 2.28	29/ 29/ 28	21/8/ 21/8/ 18/6	25.37 ± 3.72/ 10.16 ± 2.73/ 9.29 ± 1.71 ng/ml	Age, Gender, BMI	ELISA	5
Li et al. [2014][15]	CC	Asians	–/ 45.76 ± 9.41/ 48.79 ± 11.95	–/ 57/ 24	–/–/ 25/32/ 6/18	–/ 1.68 ± 0.58/ 1.04 ± 0.12 mmol/L	Age, Gender	RT-PCR	4
Zhao et al. [2014][18]	CC	Asians	5.2 ± 1.9/ 5.2 ± 1.9/ 6.3 ± 2.2	16/ 18/ 30	–/ –/ 16/14	11.32 ± 1.02/ 6.26 ± 0.97/ 4.36 ± 0.81 ng/mL	Age, Gender	ELISA	4
Xu et al. [2014][19]	CC	Asians	8.5 ± 1.5/ 8.5 ± 1.5/ 9.2 ± 1.8	27/ 27/ 25	14/13/ 14/13/ 13/12	16.64 ± 3.53/ 14.91 ± 3.24/ 13.72 ± 5.79 ng/mL	Age, Gender, BMI	ELISA	5
Li et al. [2014][21]	CC	Asians	57.8 ± 16.8/ 54.5 ± 15.3/ 50.7 ± 16.7	66/ 64/ 60	27/39/ 27/37/ 34/26	5048(2687, 8086)/ 3537(2242, 8086)/ 1023(417, 1819) pg/mL medain(min max)	–	RIA	4
Zhang et al. [2014][24]	CC	Asians	8.6 ± 2.6/ 8.0 ± 2.6/ 8.9 ± 3.0	25/ 20/ 20	12/13/ 9/11/ 10/10	9.9 ± 2.5/ 8.2 ± 1.6/ 6.2 ± 1.2 ug/L	Age, Gender, BMI	RIA	4
Yang et al. [2014][25]	CC	Asians	6.03 ± 3.02/ 5.23 ± 2.86/ 5.85 ± 3.12	15/ 31/ 19	7/8/ 14/17/ 8/11	6.51 ± 1.37/ 2.86 ± 1.27/ 1.88 ± 0.46 u	Age, Gender, BMI	ELISA	4
Rastogi MBBS et al. [2015][39]	CC	Caucasians	–/ 15.9 ± 1.7/ 16.3 ± 1.7	–/ 42/ 44	–/ 21/21/ 16/28	–/ 10.2 ± 9.5/ 10.9 ± 9.3 ng/mL	–	RIA	4
Haidari et al. [2014][40]	CC	Asians	–/ 31.28 ± 7.33/ 35.08 ± 4.87	–/ 47/ 47	–/ 26/21/ 24/23	–/ 1.41 ± 0.50/ 0.59 ± 0.19 ng/mL	Age, Gender, BMI	ELISA	6
Muc et al. [2014][47]	CC	Caucasians	–	–/ 28/ 25	–/ 11/17/ 14/11	–/ 78.12 ± 44.65/ 78.06 ± 54.65 ng/mL	–	ELISA	4
Coffey et al. [2015][36]	CC	Caucasians	–/ 32.7 ± 12.3/ 37 ± 12.1	–/ 42/ 40	–/ 15/27/ 15/25	–/ 24.9 ± 22.3/ 17.4 ± 15.3 ng/mL	Age	RIA	5
Morishita et al. [2015][37]	CS	Caucasians	6.9(2.9,15.4)/ 9.9(3.4,16.5)/ –	16/ 76/ –	12/4/ 39/37/ –	3.5(0.4, 15.3)/ 2.97(0.21, 44.1)/ – pg/mL median (min, max)	Age, Gender	IA	5

Table 1 continued

Study	Study design	Ethnicity	Case1/Case2/Control				Adjustment for confounding factors	Method Quality of testing score	
			Age(Y)	*n*	male/ female	Leptin			
Van Huisstede et al. [2015][38]	CC	Caucasians	–/ 36(19,48)/ 39(18,50)	–/ 27/ 39	–/ 7/20/ 7/32	–/ 69(18, 100)/ 55(11,100) ng/mL medain (min max)	Age, Gender	–	4
Bian et al. [2016][12]	CC	Asians	13.4 ± 3.2/ 13.2 ± 3.1/ 13.5 ± 3.4	42/ 36/ 40	27/15/ 23/13/ 26/14	10.33 ± 1.88/ 7.48 ± 0.86/ 4.36 ± 0.77 ng/ml	Age, Gender, BMI	ELISA	5
Liang et al. [2016][26]	CC	Asians	–/ 39 ± 12/ 40.4 ± 11.6	–/ 78/ 29	–/ 24/54/ 9/20	–/ 15.0 ± 10.4/ 15.2 ± 11.7 ug/L	Age, Gender	ELISA	5
Huang et al. [2016][35]	CC	Caucasians	–/ 12.4 ± 1.4/ 12.2 ± 1.5	–/ 58/ 63	–/ 29/29/ 36/27	–/ 20.0 ± 18.9/ 19.0 ± 20.4 ng/mL	Age, Gender	ELISA	5
Li et al. [2016][48]	CC	Asians	8.5 ± 2.56/ 9.1 ± 2.70/ 8.8 ± 2.46	28/ 26/ 25	15/13/ 14/12/ 13/12	19.98 ± 5.40/ 13.73 ± 2.28/ 12.17 ± 3.95 ng/mL	Age, Gender, BMI	ELISA	5
Gao et al. [2016][16]	CC	Asians	54.26 ± 11.73/ 52.64 ± 10.25/ –	34/ 11/ –	19/15/ 4/7/ –	5.98 ± 2.99/ 3.81 ± 2.29/ – ng/mL	Age, Gender, BMI	ELISA	5
Bodini et al. [2017][30]	CS	Caucasians	–/ 10.53 ± 1.96/ 10.6 ± 2.69	–/ 15/ 15	–/ 10/5/ 4/11	–/ 12.7 ± 13.2/ 11.1 ± 11.2 ng/mL	–	ELISA	4
Nasiri Kalmarzi et al. [2017][31]	CS	Asians	–/ –/ –	25/ 35/ –	–/ –/ –	50.6 ± 19.2/ 8.2 ± 6.9/ – u	–	ELISA	4
Li et al. [2018][17]	CC	Asians	–/ 45.69 ± 16.70/ 47.86 ± 13.96	–/ 50/ 25	–/ 25/25/ 12/13	–/ 5.98 ± 3.03/ 4.55 ± 2.33 ng/mL	Age, Gender, Weight	ELISA	5
Szczepankiewicz et al. [2018][34]	CC	Caucasians	9.77 ± 3.73/ 9.77 ± 3.73/ 12.6 ± 3.02	25/ 25/ 10	13/12/ 13/12/ 5/5	13.81 ± 10.56/ 10.46 ± 11.55/ 6.32 ± 5.20 ng/mL	Gender,BMI	ELISA	4
Li et al. [2019][29]	CC	Caucasians	39 ± 17/ 34 ± 13/ –	305/ 26/ –	153/152/ 11/15/ –	4.4 (2.5–4.7))/ 3.0(1.4–3.0)/ – ng/mL geometric means (IQR)	Age, Gender	Luminex xMAG	5

CC Case-control, *PC* Prospective cohort, *CS* Cross sectional, *Case1* Severe asthma, *Case2* Mild asthma, *IQR* Interquartile range, *BMI* Body mass index, *ELISA* Enzyme linked immunosorbent assay, *RIA* Radioimmunoassay, *IA* Immunoassay, *EIA* Enzyme immunoassay, *IM* Immunometric method, *min* Minimum, *max* Maximum.

predict that high level of leptin may increase the risk and severity of asthma through its interaction with obesity. Regrettably, the lack of detailed data of obesity and BMI made it unfeasible to study the influence of obesity/BMI on the association between leptin status and asthma. Further studies should be performed on this issue. Finally, leptin is also expressed in the lung and produced by the lung fibroblasts during alveolar differentiation, promoting the synthesis of surfactant protein[78]. Leptin plays a direct role in the lung development and remodeling, indicating that leptin disorder may affect the lung pulmonary homeostasis[79]. Lepin may influence the lung function, Which was consistent with our findings that leptin staus was higher in the asthma cases compared with non-asthma controls, as well as in severe asthma compared with mild asthma cases. In this sense, it is reasonable to predict that the pulmonary function may be influenced by leptin dysregulation.

Our findings for the association between leptin levels and asthma risk/progression were consistent with the above-mentioned evidence. It indicated that leptin may be a risk predictor and prognostic marker of asthma independent of age and gender. Asthma showed significantly higher leptin level than that in non-asthma controls, which might be due to the effects of leptin in the inflammation, obesity and lung development. Notably, we found that no marked difference of leptin level was observed between severe and mild asthma among Caucasians, indicating that leptin was not associated with asthma progression among Caucasians. We speculated that it may be due to the facts that Caucasians were more prone to

Table 2. Meta-analysis of the relationship between leptin status and asthma risk/progression.

Index	Studies	Q test *P*-value	Model selected	SMD (95% CI)	*P*-value
Risk					
Overall	51	$< 10^{-4}$	Random	1.061 (0.784–1.338)	$< 10^{-4}$
Caucasians	18	0.005	Random	0.287 (0.125–0.448)	0.001
Asians	32	$< 10^{-4}$	Random	1.500 (1.064–1.936)	$< 10^{-4}$
Africans	1	–	Fixed	8.386 (6.519–10.253)	$< 10^{-4}$
Progression					
Overall	25	$< 10^{-4}$	Random	1.638 (0.952–2.323)	$< 10^{-4}$
Caucasians	7	$< 10^{-4}$	Random	−0.819 (−1.998–0.360)	0.173
Asians	18	$< 10^{-4}$	Random	2.600 (1.854–3.345)	$< 10^{-4}$
Sensitivity analyses		SMD (range)			
risk					
Overall	51	0.727–1.455			
Caucasians	18	0.085–0.502			
Asians	32	0.829–2.014			
Progression					
Overall	25	0.682–2.568			
Caucasians	7	−2.572–0.692			
Asians	18	1.548–3.528			

SMD Standard mean difference.

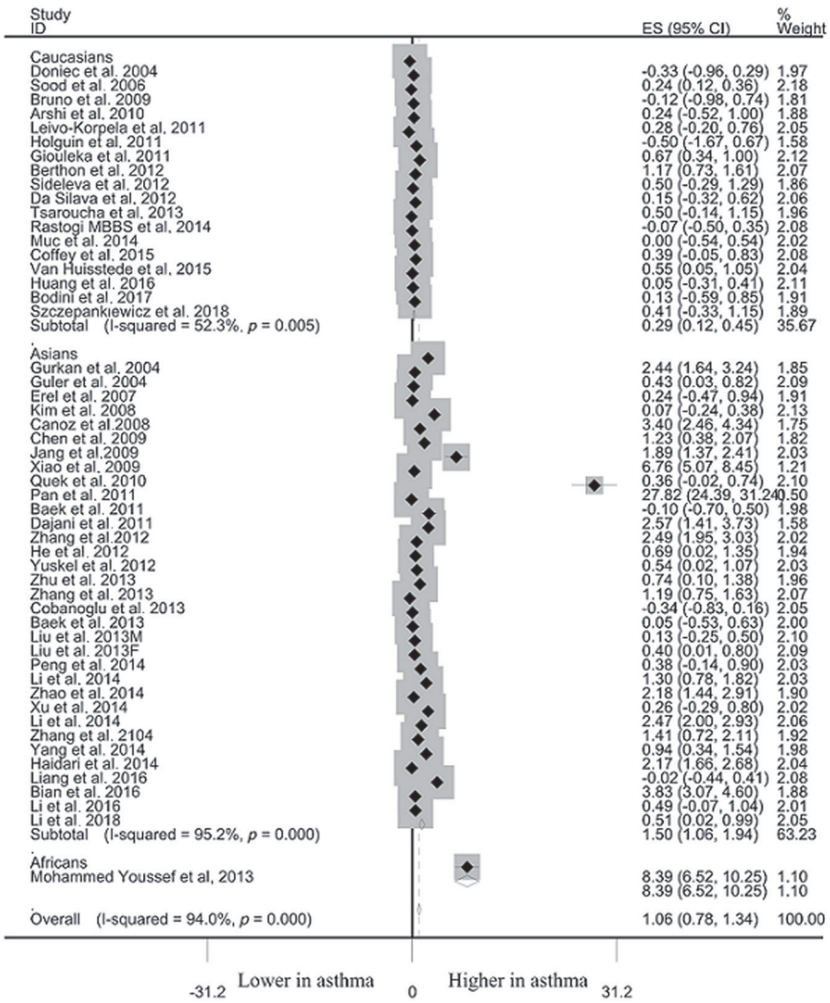

Fig. 2 Differences of leptin status between asthma and controls.

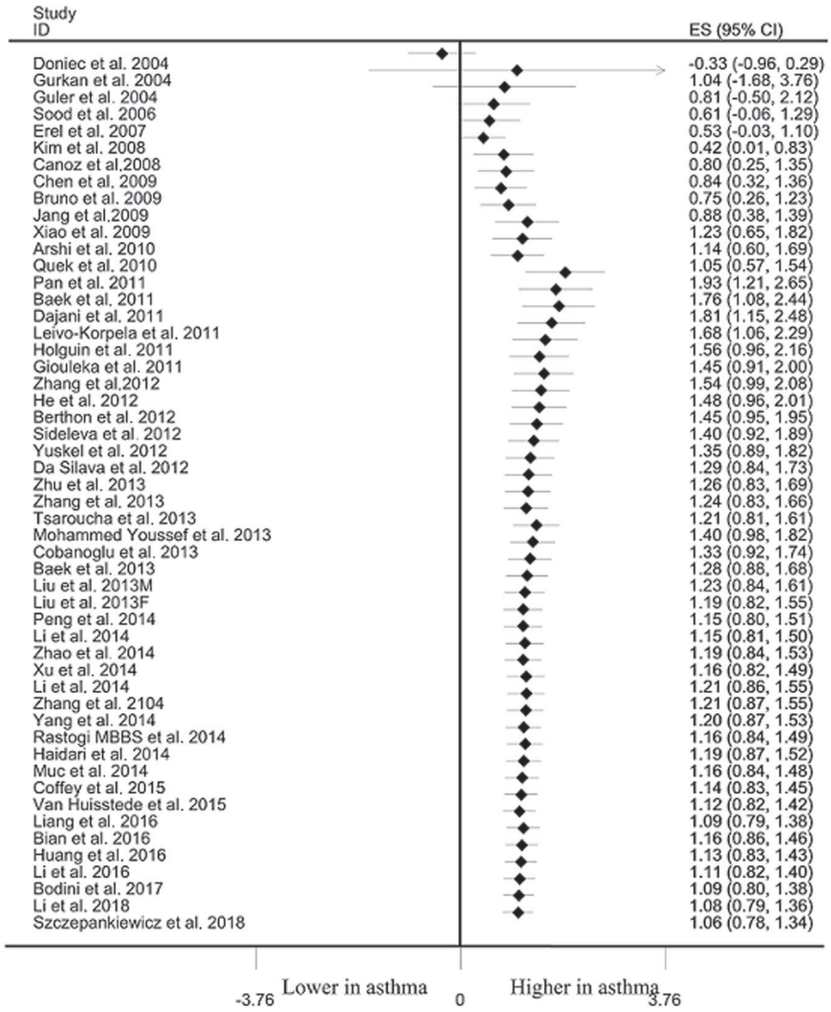

Fig. 3 Cumulative analysis of the differences of leptin status between asthma and controls.

be obese than other populations, and obesity may be associated with high level of leptin. It may lead to the comparatively similar leptin level between severe and mild asthma. On the other hand, only seven studies were recruited for the analysis of the difference of leptin level between severe and mild asthma among Caucasians, which may reduce the statistical power. Further larger number of participants should be involved in the future studies to verify our findings. Nevertheless, no marked publication bias was observed in the studies regarding the difference of leptin level between severe and mild asthma among Caucasians, which indicated that our finding was comparatively robust. Interestingly, we found that age and gender did not affect the differences of leptin levels between asthma and non-asthma, as well as severe and mild asthma, which indicated that leptin status was associated with asthma risk/progression independent of age and gender. Early monitoring and intervention of leptin level may be of great clinical implications.

Our study has obvious strengths. For example, the enrolled subjects were from different regions and the quality of the included studies was comparatively high, which increased the statistical power and promoted the generalization of our conclusions, which made the risk prediction for asthma susceptibility and progression possible. On the other hand, the analysis of the potential role of age and gender in the association between leptin status and asthma also provided a comparatively robust conclusion. Meanwhile, several limitations merited attention in our pooled analysis. First, the heterogeneities among included studies might affect the results of our investigation, although a random-effects model had been performed. Publication bias was also observed. Nevertheless, the sensitivity analyses did not change the overall results, cumulative analyses also showed a similar trend to our results and meta- regression also excluded the possibility of the influence of age and gender in our results, which proved that our conclusions were comparatively solid. Second, the study design of recruited paper were mainly case-control, which may lead to the recall bias, the disease course and medications may also affect the results. Due to the limit of available data, the in-depth analysis was not performed. Hence, further larger number, prospective studies with controlling confounding factors should be performed in the future. Third, obesity and BMI may influence the leptin level, higher leptin level was usually observed in obesity and high-BMI cases. Many asthma cases were obese than non-asthma controls, and obesity was also a risk factor for asthma susceptibility and progress. We also found that asthma cases had higher level of BMI in some of the included studies, while there were no differences of obesity ratio and BMI between asthma and controls in some of enrolled participants. The unavailable detailed data of BMI and obesity made it not possible to perform the in-depth influence of obesity and BMI on the association between

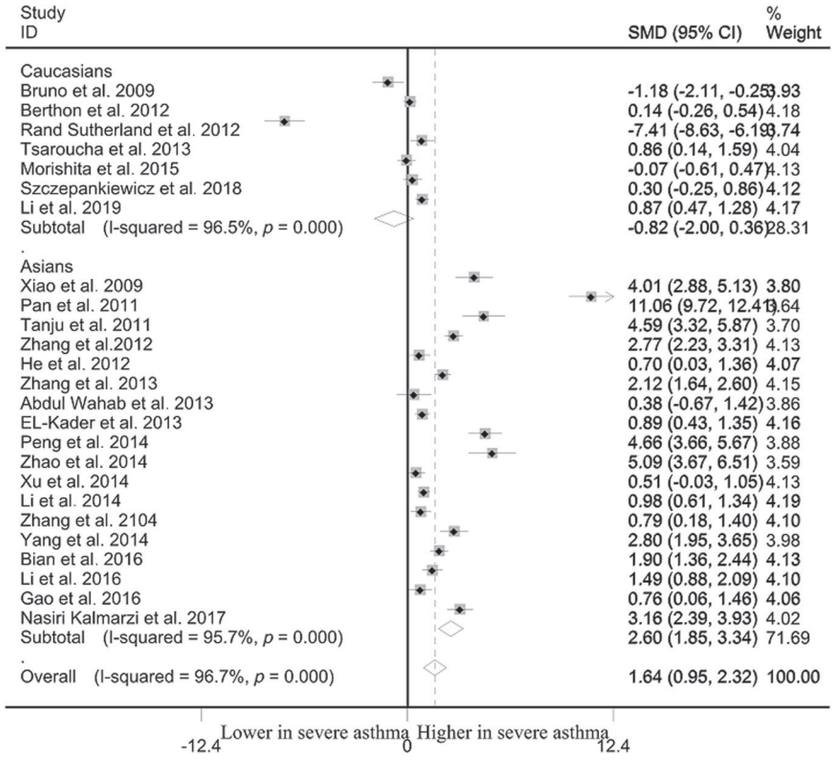

Fig. 4 Differences of leptin status between severe and mild asthma.

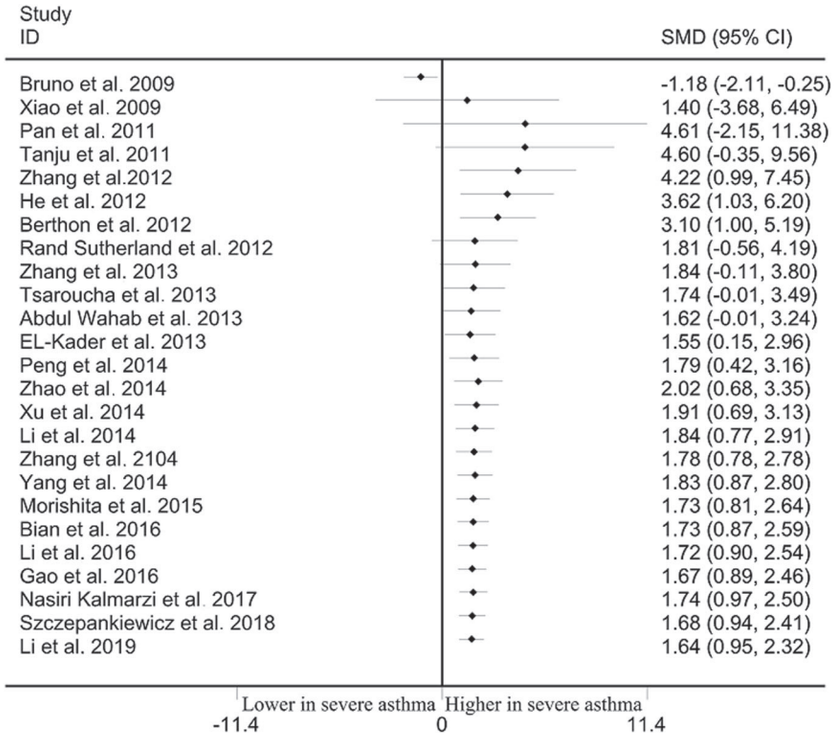

Fig. 5 Cumulative analysis of the differences of leptin status between severe and mild asthma.

leptin level and asthma. Nevertheless, our findings still had important implications that leptin level may be an auxiliary indicator for asthma susceptibility and progress due to the facts the some severe asthma cases were not obese and comprehensive analysis of multiple factors may be a better choice. Meanwhile, further multiple regression analysis involving multiple risk factors for asthma susceptibility and progress may needed in the future.

Table 3. Meta-regression analysis of the variables in the association between leptin status and asthma risk/progression.

Variable	Coefficient	95%CI	*P*
Risk			
Age	−0.031	−0.123–0.061	0.495
Male/female ratio	0.172	−2.445–2.789	0.895
Progression			
Age	−0.072	−0.208–0.063	0.279
Male/female ratio	2.373	−0.414–5.161	0.090

CI Confidence interval.

Finally, although a total of 59 studies were included in our studies, the number of studies regarding the difference of leptin level between severe and mild asthma among Caucasians was relatively small, which may decrease the statistical power. Larger number of participants with different ethnicities should be involved in the further studies to verify our findings.

In terms of our findings, further investigations may be performed to focus on the following issues: (1) elucidation of the detailed mechanism behind leptin and asthma risk/progression, (2) in-depth analysis of the association of disease course and medications with leptin status, (3) long-term, continuous observation of the changes of leptin status in asthma with a favorable study design.

CONCLUSION

Our study indicated that asthma had significantly higher level of leptin than that in non-asthma controls among overall populations, Caucasians, Asians and Africans. Severe asthma cases showed markedly higher leptin level than that in mild cases among overall populations and Asians. Our findings were of great implications that leptin may be a risk predictor and prognostic marker of asthma. Early monitoring and intervention of leptin may be needed for asthma.

DATA AVAILABILITY

The data was extracted from the public databases, including PubMed, Embase, Cochrane and Chinese WanFang databases. The readers can obtain the data from these public databases. The extracted references articles were all in the reference list of the manuscript. Furthermore, the data will also be shared by the corresponding author upon the scientific request of the readers.

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AUTHOR CONTRIBUTIONS

J.W., S.M., and W.S. participated in the conception and design of the study. S.M. and R.Z. participated in the extraction and analysis of data. S.M. participated in the interpretation of data and writing of the paper. R.Z. participated in the English editing of the manuscript. All authors approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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The feasibility and impact of implementing a computer-guided consultation to target health inequality in Asthma

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Greater Manchester has a greater prevalence and worse asthma outcomes than the national average. This study aims to evaluate a digital approach to primary care asthma management and in particular the initial impact of implementing Clinical Decision Support System software in the form of a computer-guided consultation (CGC) in the setting of primary care asthma reviews in deprived areas of Greater Manchester. The CGC (LungHealth Ltd) is an intelligent decision support system ensuring accurate guideline-based staging of asthma and assessment of asthma control with the software subsequently prompting guideline-standard management. Patients on asthma registers in Greater Manchester Primary Care Networks were identified and underwent remote review by nursing staff using the CGC linked directly to the GP clinical system. Three-hundred thirty-eight patients (mean age 59 (SD 17) years; 60% Female) were reviewed. The CGC reported the patient's asthma control to be "Good" in 22%, "Partial" in 6% and "Poor" in 72%. ACT scores were significantly higher in those patients exhibiting "Good" and "Partial" control when compared to those with "Poor" control. The number of steroid courses and hospital admissions in the previous 12 months was significantly lower in those patients exhibiting "Good" and "Partial" control when compared to those with "Poor" control. Nineteen percent were found not to have a personalised asthma management plan during CGC review, which was alerted by the CGC and subsequently, all but 3 patients had this created on review completion (McNemar's test; $p < 0.001$). 5% were found not to have been prescribed regular inhaled steroid therapy resulting in the operator being alerted by the CGC in all cases. Overall, 44% underwent alteration in asthma therapy following the CGC review with 82% of these representing treatment escalation. An end-to-end digital service solution is feasible for Asthma within primary care and the utilisation of a CGC when conducting primary care asthma reviews increases implementation of guideline-level management thus addressing healthcare inequality while enabling identification of "high risk" asthma patients and guiding appropriate therapy escalation and de-escalation.

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INTRODUCTION

Addressing healthcare inequality is a major priority for NHS England as described in the Core20PLUS5 initiative where a key priority is chronic respiratory disease[1]. Asthma is a major cause of morbidity and avoidable healthcare utilisation in the United Kingdom with greater prevalence and worse outcomes in the more deprived areas of the country. Four of the most deprived local authorities in terms of healthcare outcomes are in Greater Manchester, which has a below average life expectancy and a greater asthma prevalence with poorer outcomes than the England average[2]. This is indicated by a higher emergency hospital admission rate and some of the highest rates of over-reliance on short acting beta agonist (SABA) medication when compared to other Sustainability and Transformation Partnerships (STPs)[3–5].

There have been a number of national asthma audits since 1963[5–11] but despite the widespread availability of evidence-based guidelines since the 1990s the findings and recommendations from these audits have remained unchanged with little evidence of improvement in care or outcomes. Common themes emerging from these audits include a failure to recognise asthma severity and to follow recognised clinical guidelines. This includes the under-prescribing of inhaled corticosteroids (ICS), inadequate utilisation of personal management plans and a lack of timely specialist referral where clinically indicated. Each subsequent audit has highlighted similar recommendations including improved recognition of the severity/risk of disease in individual patients, a structured clinical assessment, better use of physiological measurements, earlier and more consistent use of inhaled corticosteroids, patient education including written personal action plans, more robust follow-up along with involvement of specialist care when required and better adherence to asthma guidelines when prescribing. Thus, simple dissemination of such paper-based guidelines has not proved to be an effective strategy in improving patient outcomes. Indeed, the National Review of Asthma Deaths (NRAD) report from 2014 mirrored the findings of the first UK asthma deaths report more than 50 years earlier highlighting the challenge of how to improve asthma care and outcomes, particularly in areas of high deprivation[6–10].

Health Innovation Manchester, an academic health science and innovation system, was formed with the aim of bringing together health and care, industry and academia to accelerate innovation and improve the health and wellbeing of Greater Manchester's 2.8 million citizens by addressing challenges and tackling inequalities. Asthma is a priority as the Greater Manchester region carries a significant burden in the form of health inequality, which is reflected in a high number of emergency hospital admissions and significant morbidity due to asthma[10–12]. The Standardising Asthma Reviews and Reducing SABA overuse in Greater Manchester (STARRS-GM) project aims to enhance the outcomes for people living with asthma in the region through proactive identification and reviews of high-risk patients to improve their asthma management. An integral part of the project is the use of

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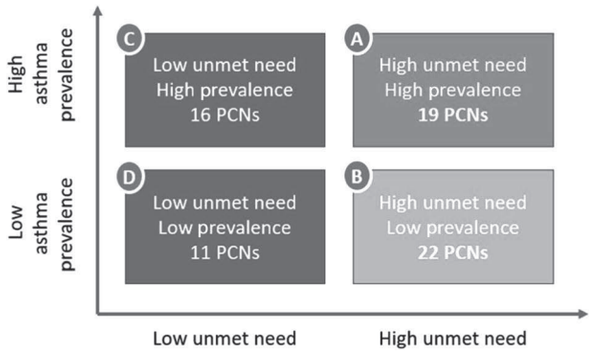

Fig. 1 Matching Asthma Need With Prevalence. Grouping of PCNs by unmet need and asthma prevalence in the STARRS-GM project.

technology including a bespoke audit tool to identify patients most likely to benefit from review and the introduction of clinical decision support system software in the form of a clinical guided consultation system (CGC). We have previously reported that the use of a CGC results in greater implementation of guideline-level care in both chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA)[13,14]. In this preliminary evaluation, we report the initial impact of implementing these technologies within primary care as part of the STARRS-GM project pathway.

METHODS

STARRS-GM Clinical pathway

The Standardising Asthma Reviews and Reducing SABA overuse in Greater Manchester (STARRS-GM) project aims to improve patient outcomes in asthma through greater implementation of guideline-level care.

The project aims to determine the reduction in SABA usage and unscheduled healthcare utilisation resulting from the implementation of the pathway. The project aims to identify and subsequently optimise asthma management in "high risk" patients as defined by patients who have received 6 or more SABA inhalers in the previous 12 months and who also had at least one NRAD risk criteria and prompt appropriate specialist asthma multidisciplinary team (MDT) input[6]. A second group of patients with good asthma control on high-dose inhaled steroid were also reviewed. This group may be on higher levels of treatment than they necessarily require and a targeted review of this group may result in de-escalation of therapy in some patients reducing potential drug side effects for the individuals while releasing resource that could be used elsewhere in asthma care.

Primary care networks (PCNs; referring to a group of primary care practices within a given locality working towards common healthcare outcomes) in the Greater Manchester area were approached to take part in the STARRS-GM project and prioritised based on asthma prevalence and level of unmet need. "High asthma prevalence" was defined as >2600 asthma patients on the Quality and Outcomes Framework (QOF) register, while "high unmet need" was defined as 60+ percentile SABA use as a proportion of total SABA plus inhaled corticosteroid use when compared to all other PCNs in England. In order to meet the Core20PLUS5 agenda PCNs in groups A and B were prioritised (Fig. 1)

To meet the objectives of the STARRS-GM project by reviewing patients either at risk of poor outcomes because of their asthma or those where step down of therapy may be possible, two groups of patients were identified using a bespoke MIQUEST (Morbidity Query Information Export SynTax)©/SNOMED (Systematised Nomenclature of Medicine Clinical Terms)© Software tool. GP systems are constructed to allow bespoke searches and this tool examines the GP asthma register pulling out all key disease features including medication, clinical events and review history. The Software collects information on the prescriptions made by the GP, though not those filled by a pharmacy (Box 1).

Box 1 Features of the Asthma computer-guided consultation (CGC)

Asthma CGC guides the healthcare professional through a number of sections incorporating the following components

- Staging of the patient's asthma treatment according to the BTS SIGN guidelines (https://www.brit-thoracic.org.uk/news/2019/btssign-british-guideline-on-the-management-of-asthma-2019/)
- Assessment of asthma control using a multi-dimensional algorithmic process taking account of established questionnaire and physiological criteria (e.g. Asthma Control Test, peak flow readings, previous healthcare utilisation) used in combination with control being divided into "Good", "Partial" and "Poor"
- Identification of key trigger factors (including occupation) for asthma and presence of cardinal "red flags" in the asthma history e.g. history of mechanical ventilation due to asthma
- Assessment of adherence to medications including the functionality to link to the number of SABA inhalers collected by the patient (using the MIQUEST© toolkit) and inhaler technique check
- Recording and intelligent interpretation of key physiological measurements such as Exhaled Nitric Oxide (FeNO) incorporating this into a therapy de-escalation algorithm
- Alerting the operator to a patient meeting NRAD criteria risk factors for future adverse asthma outcomes and highlighting those patients requiring earlier follow up
- Prompting the operator to escalate or de-escalate asthma therapy where appropriate based on key components of the CGC review and prompting need for specialist referral based on BTS SIGN guidelines
- Highlights guideline-based non-pharmacological therapy e.g. formulation of written personalised asthma management plans and discussion of smoking cessation where appropriate

Here, patient identification was conducted utilising a SNOMED/MIQUEST risk stratification tool followed by a nurse case notes review confirming the patient selection and allocation to a group.

Cohort 1: Patients deemed at "high risk" of adverse asthma outcomes i.e., those collecting 6 or more SABA inhalers in the previous 12 months together with at least one of the following additional NRAD "at risk" criteria highlighted below were identified:

- Hospital admission as a result of their asthma in the last 12 months
- Attendance at out of hours (OOH) and/or Emergency Department (ED) with an asthma exacerbation
- Two or more short courses of prednisolone for asthma in the previous 12 months
- Under-use of preventer medication (defined as <75% of recommendation)
- No recorded inhaler technique or inhaler technique recorded as poor
- No record of an annual review for their asthma

Cohort 2: Patients on high-dose inhaled corticosteroid therapy with all the following criteria were identified as potentially suitable for de-escalation of anti-inflammatory therapy:

- No exacerbations in the previous 12 months
- Asthma Control Test controlled upon last review with a score >19[15,16]
- No hospital admissions in the previous 12 months
- No ED or OOH attendances for asthma in the previous 12 months

Eight practices from 3 PCN's participated. All asthma patients from the practices were identified, a profile was run and those in the two cohorts began to be invited for asthma consultations using the practices' standard means of contacting their patients. Consultations were conducted remotely by secure video calls using the standard Accurx© platform. If patients did not have a "smart-phone" or other video capable device, a telephone review

Table 1. Asthma control at each BTS/SIGN therapy stage.

Asthma stage by CGC (BTS/SIGN guidelines)	CGC reported "Good" control ($n = 75$)	CGC reported "Partial" Control ($n = 19$)	CGC reported "Poor control" ($n = 244$)
Non-guideline therapy ($n = 1$)	0	0	1
Intermittent reliever therapy i.e., as needed SABA ($n = 16$)	2	2	12
Regular preventer therapy i.e., low-dose ICS ($n = 48$)	14	8	26
Initial Add-On therapy ICS/LABA ($n = 33$)	6	6	21
Additional Controller therapy ($n = 93$)	31	1	61
Specialist Therapies (as per BTS SIGN guideline) ($n = 147$)	22	2	123

was offered. Patients without telephones were identified for a traditional review and have not been included in this report. Patients were reviewed by respiratory trained primary care specialist nurses (National Services for Health Improvement Ltd) utilising an asthma-specific computer-guided consultation (LungHealth Asthma CGC). All patients gave individual consent to review using this CGC and to the holding of their data, including pooled anonymous data to be used for reports and research. The work was discussed with the Health Research Authority who indicated that they regarded this as a service development and that ethics approval was thus not required.

The LungHealth Asthma computer-guided consultation (CGC)

The CGC (LungHealth Ltd) enables an intelligent structured electronic asthma review. It can be used to review patients remotely or face to face. Using the medical model and constructed to reflect evidence-based guidelines, natural consultations flows are followed but with standardisation. Algorithms are embedded in the software and these prompt supplementary questions and management considerations, which are individualised to every patient dependent upon their response to questions (see Box 1) and may be customised to local guidance priorities such as medicines management. The CGC leads the healthcare professional and the patient through a structured asthma review, asking questions to enable the determination of triggers, asthma control and severity and so leading to prompts around the best treatments (pharmacological and non-pharmacological) for every individual. Although the CGC "suggests" management options, the final decision about how to manage the patient remains with the healthcare professional.

The CGC produces an electronic report that can be written back into the Electronic Health Record (EHR) for the systems commonly used in the UK. In the UK, this also populates the fields necessary for the quality and outcomes framework. The CGC is hosted on a local UK NHS server and has two-way connectivity with the primary care server. Its use is password protected enabling Caldicott principles and General Data Protection Regulations to be satisfied thus ensuring patient data gathered during consultations is duly and lawfully protected and that these data are only used when it is appropriate to do so, with anonymity being preserved[17] (https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/).

Statistical analysis

Statistical analysis was performed using SPSS 28.0. Data are presented as mean ± SD unless otherwise stated. Statistical significance was defined as a p-value < 0.05. We used the independent sample t-test to identify significant differences in continuous variables and the Chi-squared test for categorical variables. The McNemar's test was used to determine significant differences on a dichotomous dependent variable between paired data.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

RESULTS

The eight practices had 76,270 patients on their lists with 4791 identified as having asthma. At the cut point for analysis 338 patients had received a guided consultation. Of them 291 fell into cohort 1, 29 into cohort 2 and 18 patients with asthma but not in the two groups also received a review; the practices confirm the last group were contacted in error.

A total of 338 patients (mean age 59 (SD 17) years; 60% Female) on the GP asthma register in one of the two cohorts described above were identified using the Miquest toolkit and underwent CGC review. CGC review enables the identification of patients according to BTS/SIGN therapy stages[16]. The CGC characterised the patients' asthma control using ACT/RCP/GINA to be "Good" in 22% ($n = 75$), "Partial" in 6% ($n = 19$) and "Poor" in 72% ($n = 244$). The level of asthma control for patients in each of these BTS therapy stages (https://www.brit-thoracic.org.uk/news/2019/btssign-british-guideline-on-the-management-of-asthma-2019/) is shown in Table 1.

The relationship between the CGC definition of asthma control with key multi-dimensional components comprising the assessment of asthma control as well as SABA use is illustrated in Tables 2 & 3.

The ACT scores were significantly higher in those patients exhibiting "Good" and "Partial" control when compared to those with "Poor" control ($p < 0.001$). The number of oral corticosteroid courses in the previous 12 months was significantly lower in those patients exhibiting "Good" and "Partial" control when compared to those with "Poor" control ($p < 0.01$) and ($p < 0.001$), respectively.

Hospital admissions in the previous 12 months were significantly lower in those patients exhibiting "Good" and "Partial" control (none in both of these groups) when compared to those with "Poor" control (13 patients were admitted to hospital in this group; $p < 0.001$).

Overall, the mean number of SABA inhalers prescribed for the patients was significantly higher compared to the number reportedly used by the patient over a 12-month period (8.92 (SD 3.88) v 7.84 (SD 5.23); 95% CI 0.36 to 1.80; $p = 0.003$). The number of SABA inhalers used in the previous 12 months was significantly lower in those patients deemed to "Good" control by the CGC compared to those deemed to have "Poor" control in those where this data was collected by the CGC (see Table 3). The same relationship was observed in terms of the number of SABA inhalers collected by the patient with a significantly lower number collected in those with "Good" control. The number of preventer

Table 2. Relationship between CGC definition of asthma control and clinical parameters.

	"Good" control ($n = 75$)	"Partial" control ($n = 19$)	"Poor" control ($n = 244$)
ACT score (mean/SD)	23.23 (1.49) ($p < 0.001$)[a]	21.32 (1.60) ($p < 0.001$)[a]	15.71 (4.11)
Number of oral corticosteroid courses in previous 12 months (mean SD)	0 (0) ($p < 0.001$)[a]	0.53 (1.35) ($p < 0.01$)[a]	1.41 (2.34)
Number of hospital/ED visits in previous 12 months (mean SD)	0 (0) ($p < 0.01$)[a]	0 (0) ($p < 0.01$)[a]	1.92 (1.66)

[a]McNemar's test when compared with poor control.

Table 3. Relationship between CGC definition of asthma control and inhaler use.

	"Good" control	"Poor" control	*p*-value
SABA prescribed	7.85 (3.81) ($n = 74$)	9.36 (3.92) ($n = 240$)	$p = 0.004$
SABA reported as used	4.94 (3.55) ($n = 54$)	8.74(5.42) ($n = 223$)	$p < 0.001$
Preventer inhaler prescribed	7.84 (4.35) ($n = 75$)	8.32 (4.19) ($n = 241$)	$p = 0.37$
Preventer inhaler reported as used	7.51 (4.34) ($n = 74$)	8.00 (4.00) ($n = 237$)	$p = 0.39$

inhalers prescribed in the previous 12 months did not significantly differ in those patients deemed to have "Good" control by the CGC compared to those deemed to have "Poor" control.

Review using the CGC highlighted three patients who had previously been intubated and ventilated due to asthma. Despite asthma control currently being "Good" in one of these patients, the CGC flagged up the previous history and alerted the operator that this patient should be considered for specialist follow up.

Table 4 summarises some key outcomes resulting from the CGC review. 66 (19%) patients were identified as having no written personalised action plan and following CGC review, this was achieved in all but 3 patients (McNemar's test; $p < 0.001$).

Eighty-five patients (25%) were identified as being current smokers and the CGC prompted nurses to deliver smoking cessation advice for all these patients though only 4 patients agreed to be referred for further support.

Of the 16 patients identified as being prescribed "salbutamol only" and the one patient on a non-guideline regimen (see Table 1), all but 3 patients were started on inhaled corticosteroid therapy following CGC review (McNemar's test; $p < 0.001$). Of these 16 patients on salbutamol only, mean 12-month SABA inhaler use was 6.00 (SD 4.02) and ACT score 18.38 (SD 3.54) with asthma control deemed by the CGC to be "Poor" in 12 of these 16 patients.

71% (240/340) of patients undergoing CGC review were staged either at "Specialist therapies" or "Additional Controller" stage (see Table 1). The CGC determined asthma control to be "poor" in 77% (184/240) of this sub-group and in all cases prompted the operator to consider referral for specialist assessment.

Overall, CGC review recommended a change in asthma therapy in 44% (149/338) of patients with 82% ($n = 122$) of these changes representing therapy escalation. "Good" control was reported by the CGC in 75 patients (22%). The CGC prompted consideration of therapy de-escalation where appropriate in 73 of these patients with de-escalation not being appropriate in 2 patients as they were on intermittent reliever therapy. Of those 73 patients with "Good control" where the CGC recommended therapy de-escalation, the operator chose actually to de-escalate therapy in 37% ($n = 27$) after discussion with the patient's GP practice. When taking this "Good control" group, 22 patients were on "Specialist Therapies" of whom 8 were de-escalated and 31 where on "Additional Controller" therapy of whom 14 were de-escalated.

DISCUSSION

This initial evaluation of the STARRS-GM approach was undertaken to determine the feasibility of this comprehensive digital approach and particularly the utility of the LungHealth asthma computer-guided consultation (CGC). Health informatics and multiple deprivation index metrics were utilised to select one of the most deprived areas and the primary care networks serving Greater Manchester. This allowed the identification of a PCN with the challenge of excessive SABA use and poor asthma outcomes.

In this PCN the bespoke MIQUEST/SNOMED search tool was used to identify two cohorts of patients for review, the LungHealth asthma guided consultation was then utilised. The results show that the approach is practical. When the 338 patients receiving the guide consultation are considered, the first observation is that the CGC characterised patients grouping them into levels of control (as seen in Table 1) suggesting that use of the MIQUEST/SNOMED tool could be used to correctly prioritise selected patients for review using the guided consultation. At this point we recognise that only a proportion of the population has been evaluated. It is possible that in the whole cohort the tool would prove to be less specific, however, this data gave us enough assurance to continue the project with this search methodology. The consultation was also seen to be adept at identifying issues with care, which may lead to excessive SABA use and poor asthma control and identifying gaps in patient care. In addition to identifying and addressing gaps in their care such as 19% not having written action plans or the poor adherence in 18.5%, use of the CGC also prompts medication changes towards guideline management, though the healthcare professional does make the final decision as described. 44% of those reviewed had medication changes recommended with a step up in 82% and a step down in 18%. Referral for specialist assessment was also suggested in a significant number of patients though it must be noted that the population studies here is a subset of those on asthma register and many patients were selected for review because they were identified as being poorly controlled.

In primary care services, healthcare professionals are faced with the challenge of implementing an increasing number of complex clinical guidelines from different specialties to deliver optimal patient outcomes[18]. However, despite an emphasis on the importance of guideline-standard care, it is apparent that in conditions such as asthma the strategy of guideline dissemination in the hope of this translating into clinical benefit has yielded limited success. For example, while it is evident that the use of written personalised action plans and patient education leads to a significant reduction in healthcare utilisation, the implementation of this key practice point has been historically low, a finding mirrored here where 19% of patients were lacking a personalised action plan[19,20]. However, following CGC review, this had been achieved for nearly every patient in this cohort suggesting that the introduction of such intelligent clinical decision support system software into patient pathways may lead to a greater uptake of evidence-based practice, upskilling healthcare professionals and reducing variation in the delivery of care as has been demonstrated previously in the setting of COPD and OSA[13,14]. The CGC assesses asthma control using a multi-dimensional

Table 4. Management changes prompted by CGC.

	Number identified by CGC	Action following CGC review
Absence of a written personal action plan	66 (19%)	63 given personal action plans
No regular 'Preventer'	17 (5%)	14 prescribed regular inhaled steroid therapy
Inadequate inhaler technique	31 (9%)	21(6%) in whom a spacer was added.
Poor adherence	63 (18.5%)	Importance of adherence and reasons for poor adherence discussed with all
Current smokers	85 (25%)	All prompted regarding Smoking cessation and invited to be referred to local smoking cessation services
Sub-optimal Asthma control at the "Specialist therapies" and "Additional Controller" stage meriting consideration of specialist assessment	184 (77%) had "poor" control	Prompt to consider referral for specialist assessment.

framework incorporating validated tools such as the ACT, assessment of adherence and physiological indices such as lung function and its algorithms also prompt the operator to consider asthma triggers and suspected occupational factors during review. All this ensures that patients with symptoms of uncontrolled asthma are not missed during a CGC consultation and are highlighted to the operator for further action. The National Review of Asthma Deaths stressed the need for patients to adhere to regular inhaled corticosteroid medication in order to maintain good asthma control and prevent deaths[6]. The use of the CGC highlighted 5% of patients who were found not to have been prescribed regular inhaled corticosteroid therapy despite the majority of this sub-group having poorly controlled asthma at the time of review. Following CGC review, all but one of these patients were commenced on regular inhaled corticosteroid therapy thus reducing the risk of future harm due to uncontrolled asthma. The finding of excess SABA use in a patient also represents a risk factor for future asthma attacks and national guidance states that the identification of this future risk is an important component in the delivery of personalised asthma care[6] (https://www.brit-thoracic.org.uk/news/2019/btssign-british-guideline-on-the-management-of-asthma-2019/). Meeting this requirement is an area integral to CGC functionality as its algorithms alert the operator to those patients who meet guideline thresholds for excess SABA use and inhaled corticosteroid underuse.

Another important deficiency in asthma care that has come under recent scrutiny concerns the failure of healthcare professionals to recognise severe asthma in a timely and appropriate manner and trigger referral for specialist assessment according to guideline-based practice. This is particularly apparent with the advent of biologic therapies[21–23]. The implementation of the CGC resulted in three quarters of the cohort in the "specialist therapies" stage" or at the "additional controller" stage being identified as sub-optimally controlled. The CGC works to prompt specialist referral in such cases while also taking into account other modifiable factors such as adherence and any acute precipitating factors. At the opposite end of the spectrum, there remains a reluctance to de-escalate treatment in asthma where it is safe and clinically appropriate to do so thus risking adverse clinical and health economic consequences, e.g., side effects of high-dose inhaled corticosteroids[24]. The CGC prompted consideration of de-escalation in most cases where it deemed asthma control to be "good" with the operator actually de-escalating therapy in 37% of these cases. A 6-month prospective Dutch study focusing on severe asthma demonstrated that encouragingly, the use of an internet-based tool incorporating fractional exhaled nitric oxide (FeNO) levels and asthma control questionnaire (ACQ) resulted in a reduction in steroid dose (median cumulative steroid dose was 205 mg lower in the intervention group) without a deterioration in asthma control[25]. Our evaluation did not utilise FeNO measurements when stepping down therapy on this occasion but did reveal a significant difference between the number of reliever inhalers collected and those actually used. While these data are limited by self-reporting actual inhaler usage, it raises the important issue regarding the health economic impacts of medicines wastage and encourages development of strategies to address this issue[26].

The role of clinical decision support software (CDSS) in the assessment of adult asthma in the UK has been described previously in the literature[27,28]. A Canadian study reported the impact of CDSS software on the uptake of asthma action plans and reported an increase in uptake from 0 to 17.8% and an increase in the proportion undergoing assessment of asthma control with a proportion of patients having therapy escalated compared[27]. One difference between the CDSS evaluated by these authors and that reported here is that in the latter, assessing asthma control is mandatory in order to complete the consultation. A critique of CDSS applicability in asthma published in 2014 commented that the effectiveness of such technology was found to be limited at the time due to the system's recommendations not always being followed and a paucity of use[28]. However, since then, the increasing imbalance between capacity and demand within healthcare systems alongside the challenges posed by the COVID-19 pandemic has created new opportunities for the development and evolution of such digital solutions particularly when systems are fully integrated within the primary care EHR as in the case of the CGC reported here. Importantly, the remote capability of the CGC coupled with direct two-way connectivity to the primary care server enables elective primary care reviews to continue during pandemic conditions as patients may undergo such reviews from home and indeed healthcare professional can also work remotely if required.

This service evaluation carries some limitations in terms of extrapolation to wider clinical practice. All patients undergoing review with the CGC were on the GP asthma register with a primary care diagnosis of Asthma. It is recognised that there are patients on primary care Asthma registers who may not have a true diagnosis of Asthma and this evaluation does not take such a cohort into account[29]. However, the CGC is currently being further developed to consider important differential diagnoses and the presence of atypical symptoms in patients with a less certain asthma diagnosis. Further studies are required in this area to determine diagnostic validity in this setting.

The importance of appropriate use of and adherence to asthma medications cannot be overemphasised in clinical practice. The implementation of this CGC with the existing linkage to the primary care server and the MIQUEST© tool enables those patients who are deemed at being high risk of adverse asthma outcomes (e.g., excess SABA use and underuse of inhaled corticosteroids) easily to be identified and invited for a structured CGC review. Where poor adherence was addressed by patient education on the benefit of regular medicines, reinforcing self-management,

addressing inhaler technique and arranging earlier follow up. However, at present, any benefit of the CGC in adherence assessment may be limited by the subjective account of actual inhaler use. Future clinical pathways may be enhanced further with the application of "e-inhaler" technology in selected "high risk" patients following CGC review and this area requires also detailed prospective study[30]. The use of FeNO in the assessment and management of asthma is gaining prominence within primary care and while the CGC enables the operator intelligently to interpret FeNO readings during a consultation both diagnostically and to aid therapy de-escalation, this was not evaluated in this preliminary analysis[31]. The two cohorts evaluated here represent a group in a PCN with a high deprivation index and in addition satisfied the priority of Health Innovation Manchester STARRS-GM project meeting high-risk criteria for adverse asthma outcomes or suitability for therapy de-escalation as opposed to an unselected asthma population. Nevertheless, it is clear this targeted approach is feasible and the scale of changes suggest beneficial outcomes can be envisaged and a roll out to an additional seven PCN's is currently underway. As this is a preliminary cross-sectional analysis, we describe the management changes but not the clinical consequences of implementing the changes recommended resulting from the CGC review and a further longitudinal evaluation is planned aiming to measure the impact of this pathway in terms of reduction in SABA use, healthcare utilisation and hospitalisation due to asthma including outcomes in the cohort where de-escalation of therapy occurred.

The CGC was used here in a remote fashion by trained respiratory nurses based in primary care, but future service evaluations will involve use by practice nurses. Such an evaluation will also incorporate and define the training needs of practice nurses and General Practitioners in order to gain competency in the use of the CGC in such a pathway. Already available is an online training portal and a test site for users to enter test patient. We do recognise some users may require mentorship support in the first 1–2 clinics. Detailed longitudinal studies are also required to measure the health economic impact of such technology in primary care asthma management alongside any clinical benefits.

We have demonstrated that an end-to-end digital service solution is possible from the recognition of PCNs for prioritisation based on deprivation and/or poor asthma outcomes through to the identification of priority patient groups for review where there is the most gain. The introduction of clinical decision support software in the form of a computer-guided consultation when conducting asthma reviews within primary care is feasible. Not only this, but its use leads to management change in the majority of patients reviewed and the increased implementation of guideline-level standard of care, which is integral to improving patient outcomes and reducing health inequality.

DATA AVAILABILITY

The datasets generated during and analysed during the study are not publicly available due to ethical reasons but are available in an anonymised format from the corresponding author on request.

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AUTHOR CONTRIBUTIONS

The service pathway was designed by B.K., E.M., B.C., C.B., and J.C. The guided consultation was created and programmed by B.C., D.L., P.E., L.R., M.O., L.D., R.M.A., M.P., and E.M. All authors were involved in the analysis and interpretation of the data as well as preparing and then drafting the manuscript.

COMPETING INTERESTS

The CGC has been developed and owned by LungHealth Ltd. Drs. Chakrabarti, Angus, Davies, Professor Pearson and Mr. McKnight are all directors of LungHealth Ltd and were all involved in the development of the CGC. B.K., C.B., J.S., D.L., P.E., M.O., L.R. have no competing interests to declare. The STARRS-GM project has been developed as part of a Joint Working initiative between HInM (Health Innovation Manchester) and AstraZeneca UK. As part of this Joint Working Agreement, Astra Zeneca UK funded the licenses for the use of the LungHealth software, project management costs and the nurse resource to deliver clinics and to perform the initial audit and case-finding.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41533-023-00329-8.

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Prevenar13 sikkerhetsinformasjon
Indikasjon: Aktiv immunisering for foreygging av invasiv sykdom og pneumoni forårsaket av Streptococcus pneumoniae hos voksne ≥18 år og hos eldre. Bruk av preparatet bør baseres på offisielle anbefalinger. Dosering voksne ≥ 18 år: Én enkeltdose gis ved intramuskulær injeksjon. **Kontraindikasjoner**: Vaksinasjon skal utsettes ved akutt, alvorlig febersykdom. Mindre infeksjoner som forkjølelser skal imidlertid ikke gjøre det nødvendig å utsette vaksinasjonen. Kontraindisert ved overfølsomhet for virkestoffene eller difteritoksoid. **Forsiktighetsregler**: Egnet medisinsk behandling og overvåkning skal alltid være tilgjengelig i tilfelle sjeldne anafylaktiske reaksjoner oppstår etter injeksjon. **Interaksjoner**: Prevenar 13 kan gis samtidig med sesongens kvadrivalente, inaktiverte influensavaksine (QIV). **Viktige bivirkninger:** Overfølsomhetsreaksjoner, anafylaktisk/anafylaktoid reaksjon inkludert sjokk er rapportert, se også Forsiktighetsregler. **Pris**: 698,20 kr. Reseptgruppe C.

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REVIEW ARTICLE OPEN

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Addressing sex and gender to improve asthma management

Louis-Philippe Boulet[1]✉, Kim L. Lavoie[2], Chantal Raherison-Semjen[3,4], Alan Kaplan[5], Dave Singh[6] and Christine R. Jenkins[7]

Sex (whether one is 'male' or 'female', based on biological characteristics) and gender (defined by socially constructed roles and behaviors) influence asthma diagnosis and management. For example, women generally report more severe asthma symptoms than men; men and women are exposed to different asthma-causing triggers; men tend to be more physically active than women. Furthermore, implicit, often unintended gender bias by healthcare professionals (HCPs) is widespread, and may result in delayed asthma diagnosis, which can be greater in women than men. The sex and gender of the HCP can also impact asthma management. Pregnancy, menstruation, and menopause can all affect asthma in several ways and may be associated with poor asthma control. This review provides guidance for considering sex- and gender-associated impacts on asthma diagnosis and management and offers possible approaches to support HCPs in providing personalized asthma care for all patients, regardless of their sex or gender.

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INTRODUCTION

Globally, ~300 million people live with asthma[1]. There are well-established sex and gender differences in the prevalence of asthma: more boys than girls suffer from asthma pre-puberty, while post-puberty, the prevalence of asthma is higher in women than men[2]. Furthermore, women are more likely to have severe asthma, comorbidities, worse quality of life, and a higher rate of exacerbations, hospitalizations, and mortality compared with men[1,3]. These differences have been attributed to sex-specific physiological differences (e.g., sex hormones)[2], but may also be driven by gender-specific sociocultural and behavioral differences (e.g., gender roles/occupations, symptom perception)[4,5].

Importantly, 'sex' and 'gender' are not always clearly defined in scientific literature and are often used interchangeably and/or incorrectly[6]. Sex refers to the biological and physiological characteristics of females and males (e.g., chromosomes, hormones, and reproductive organs), while gender is a sociocultural construct that refers to the identities, characteristics, roles, and behaviors of men, women, boys, and girls and gender-diverse people[6]. Therefore, gender characteristics can vary between societies and may change over time.

In a previous review[7], we outlined current evidence for sex- and gender-related differences that influence asthma pathogenesis, clinical course, severity, symptoms, and management. The aim of this narrative review is to provide guidance for healthcare professionals (HCPs) to consider sex- and gender-associated differences in asthma diagnosis and management when deciding the best course of action for their patients. These suggestions are based on the authors' assessment of current evidence and are outlined in each section as "author guidance".

There are limited studies on gender-diverse people with asthma, and many studies have been carried out using 'traditional' sex and gender definitions. As such, we have used the terminology of 'men' and 'women' throughout this review.

GENDER DIFFERENCES IN PATIENT HEALTH BEHAVIORS

Patient reporting of symptoms

Patient reporting of symptoms may influence the way symptoms are interpreted by HCPs, and, therefore, how the patient's asthma is managed. Evidence suggests that women perceive their asthma as more symptomatic than men and report more frequent, severe, and bothersome symptoms, even if the severity and level of asthma control are similar[4]. Compared with men, women also report poorer quality of life and greater symptom impact, including more limitations on sports, social activities, sleep, and day-to-day activities[8]. It may be for these reasons that women are more likely than men to report their symptoms to a HCP[8]. Men may also understate their symptoms and be reluctant to seek HCP support due to societal expectations that men should not complain about their health[9].

Author guidance:

- Recognize that men and women may present with different symptom profiles and that gender can affect how and when patients report their symptoms.
- Confirm diagnosis with spirometry[10], and use validated measurements of asthma control e.g., asthma control questionnaire or asthma control test, which help to objectively assess the severity of patients' symptoms and response to treatment[10].
- Discussion guides that help patients understand their asthma may prompt conversations to gain insight into their symptoms and daily life limitations so that appropriate support can be offered by HCPs and asthma educators[11,12].

Triggers and long-term exposures

While certain triggers, such as air pollution, are likely to be similar for both genders, women and men may be exposed to different triggers and asthma-causing substances due to their gender roles and occupations (Fig. 1)[5]. Globally, women are more likely to be exposed to cleaning chemicals and biomass fuels, while men are

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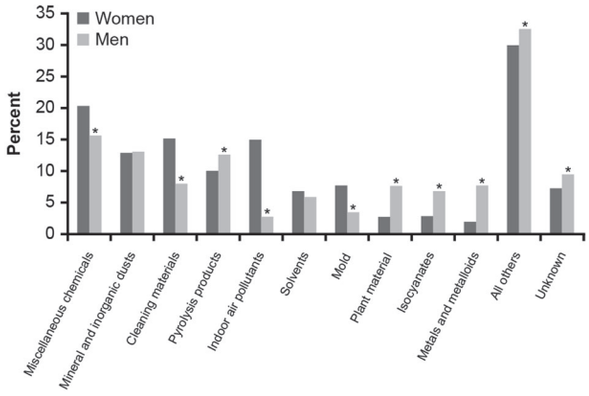

Fig. 1 Major categories for reported exposures associated with work-related asthma by gender. Categories defined by the Association of Occupational and Environmental Clinics (AOEC), September 2012[5]; *p-value for gender differences <0.05. Percentages are based on the number of females ($n = 4973$) and males ($n = 3264$). Adapted from White et al.[5]. Reproduced with permission from Taylor & Francis © 2014. www.tandfonline.com.

more likely to be exposed to pyrolysis products, plant-based materials, isocyanates, metals, and metalloids (all of which are associated with an increased risk of asthma and respiratory disease [Fig. 1])[5,13–17]. However, traditional gender roles are evolving, and it is important to explore the potential exposures faced by men and women in occupations that were once strongly aligned with a particular gender. Changing roles at work and home may result in the reduction of gender differences in exposure to asthma-exacerbating triggers.

On average, more men than women smoke[18]; however, it appears that women are more susceptible than men to smoking-related asthma symptoms[19]. Women who smoke are less likely than men to quit successfully as they are more susceptible to tobacco addiction: nicotine is metabolized faster in women than in men, resulting in a need for a higher level of nicotine to produce pleasurable feelings[20]. There may also be concerns for women surrounding cessation-related weight gain[21].

Author guidance:

- Be aware that, generally, men and women are exposed to different occupational and domestic triggers that may affect their asthma.
- Explore patient's occupation, lifestyle and history to identify possible exposure to triggers. Discuss personal behaviors, workplace strategies, and explore protective measures to minimize exposure. If asthma symptoms persist or worsen, explore possible lifestyle and occupation changes.
- Although smoking cessation may be more difficult in women than men, due to factors such as susceptibility to tobacco addiction and weight-gain concerns, it should be encouraged regardless of patient sex/gender. Men and women often have different reasons for smoking or not quitting, and motivational communication (Fig. 2[12]) could be used to understand these reasons and tailor cessation advice.

Physical activity and diet

Obesity and low levels of physical activity are associated with an increased risk of asthma symptoms[22]. Compared with women and girls, men and boys are more likely to participate in regular physical activity[23,24] and are less likely to be obese[25]. However, men may have poorer diets than women; a large study that examined the relationship between gender, sexuality, and diet, reported that "very gender conforming males" (males with more 'male' personality traits) had unhealthier diets than the other groups examined[26]. It is known that a high intake of fruits and vegetables has anti-inflammatory properties that may reduce asthma risk and improve asthma control[27], although more studies are needed on the relationship between diet and asthma outcomes.

Interventions that promote physical activity and healthy eating have been shown to improve asthma outcomes in both men and women[28]. It is important to note that men and women may have different goals and motivations for physical activity. Men have been shown to be motivated by competition, maintaining health, and enhancing body shape, whereas women are more motivated by emotional support and social aspects, as well as attaining well-being and a positive body image[29].

Author guidance:

- Promote initiatives to educate all patients on the benefits of weight control, physical activity, and healthy eating on asthma control. Guide patients towards physical activities that they find enjoyable and beneficial.

Adherence to asthma medication regimen

Taking medications correctly is important for asthma control. A Swedish study reported that, overall, men and women displayed similar levels of intentional nonadherence, but men with certain self-reported personality traits (e.g., agreeableness and conscientiousness) were more likely to adhere to their medication than men with more self-reported neurotic-type personality traits (e.g., vulnerability and self-consciousness)[30]; there was no association between personality traits and medication adherence in women[31].

Women may be more likely to use their inhalation device incorrectly, which impacts asthma control[32,33]. Moreover, many patients rely on short-acting beta-agonists (SABAs) to treat their immediate asthma symptoms rather than taking daily maintenance medications that decrease the risk of exacerbations[10,34]. A Canadian study in patients ≥66 years old reported that women filled fewer prescriptions for maintenance inhalers and more prescriptions for reliever inhalers than men, suggesting that the women may also have had poorer asthma control[31]. As some people may not take their maintenance inhalers as prescribed and instead depend on reliever medication, the Global Initiative for Asthma (GINA) 2022 report recommends (in Track 1) low-dose inhaled corticosteroid (ICS)-formoterol as needed for mild asthma, or low-to-high dose ICS-formoterol as maintenance for more severe asthma (with low-dose ICS-formoterol as needed as a reliever). A second treatment track (Track 2) is possible, but not preferred[10]. It is important to consider that communities with limited resources can be found across low-, middle- and high-income countries; for these patients, Track 1 may not be affordable, and so Track 2 may be chosen while checking for adherence to treatment[10].

Author guidance:

- Help patients to understand that asthma is a chronic condition that can be controlled by taking asthma medication as prescribed and using inhalers correctly, in combination with self-management (e.g., reducing allergen exposure, engaging in a healthy lifestyle).
- Educate patients on self-management to help them identify symptom worsening. Self-management education that includes a written action plan, regular review and symptom monitoring, reduces unscheduled visits, hospitalization and time lost from school or work[10]. A plan to explain when and how to increase medication(s) and when to seek HCP input may help patients gain greater control of their asthma, increase confidence about getting active and reduce asthma exacerbations[35].
- Assess the frequency of SABA use. In patients who are dependent on SABAs and/or are avoiding regular maintenance medication, ICS-formoterol can be used "on

Motivational communication competency	Example of using motivational communication competency
Reflective listening *Understanding and restating what the patient is saying*	"So, you're taking your asthma medication as prescribed, but you're finding that your symptoms get worse just before menstruation."
Expressing empathy *Emotionally understanding and sharing the feelings of the patient*	"You're not alone, many women express concerns about taking their daily asthma medications whilst pregnant."
Eliciting "change talk"/evocation *Helping patients recognize the advantages of, and express optimism in change*	"What do you see as the advantages of improving your level of asthma control? How would your life improve if you had fewer symptoms?"
Goal setting *Guiding the patient to set realistic goals*	"Exercise is a great way to improve your asthma control. You said you used to enjoy e.g., gym classes/yoga/tennis. What do you think would be a realistic goal to get you started?"
Demonstrating acceptance, tolerance, and respect *Demonstrating acceptance, tolerance and respect for the patient*	"Even though you are committed to better controlling your asthma symptoms, you are still concerned about side effects. You are not alone; many patients have expressed the same concerns."
Being collaborative *Involving the patient in the management of their asthma*	"It sounds like you are ready to be more physically active, we just need to figure out how to make it part of your daily routine. Could we explore some options together?"
Providing information neutrally *Giving clear, factual information*	"That's a great question. According to studies, your controller inhaler, when used as prescribed, can reduce your risk of asthma attacks by x%."
Responding to resistance *Using motivational communication to respond to resistance*	"It sounds like you understand the benefits of taking your daily controller inhaler as prescribed, but are completely overwhelmed right now, and are having trouble managing it all."
AVOID – what not to say	
Expressing hostility or impatience	"You complain about not being able to breathe and about how your asthma keeps you up at night but continue to smoke. How am I going to help you if you don't help yourself?"
Negatively judging or blaming	"If playing sports is important to you, then taking your controller inhaler as prescribed should be too."
Being argumentative or confrontational	"I know quitting smoking is hard, but you really need to quit. Smoking isn't worth putting your health at risk."

Fig. 2 Motivational communication competencies, definitions, and examples. Adapted from Gosselin Boucher et al.[12] under Creative Commons Attribution license CC-BY.

demand" in mild asthma (anti-inflammatory reliever therapy), or regularly twice-daily plus on demand if asthma is more severe[10]. For severe asthma, treatment regimens may be simplified (if considered appropriate and the patient is adherent) with a single once-daily inhaler with a long-acting (24 h) ICS/beta-agonist association, plus long-acting muscarinic antagonist if required[10,36]. Alternatively, add-on biologic therapy can be considered if these therapies are not sufficient to treat persistent symptoms, following a specialized consultation and review of potential care gaps[10].

- Assess asthma phenotype to tailor treatment and optimize asthma control.
- Check inhaler technique regularly. Poor inhaler technique is common, and contributes to poor asthma control, along with overuse of SABAs and short-course oral corticosteroids (OCS)[10,37].

GENDER BIAS IN HCP BEHAVIOR

Implicit gender bias by HCPs is widespread and may affect the diagnosis, management, and health outcomes of diseases/conditions[38]. A 2019 analysis in Denmark found that in 72% of cases (of various diseases, including respiratory diseases), the

median time span from symptom onset to diagnosis was longer in women than in men[39]. Moreover, in patients with chronic pain, men are often viewed as 'brave' while women are viewed as 'emotional' and 'complaining'[40]. In a recent survey of women in England, 84% said they felt they were not listened to by HCPs[41]. This implicit bias may prevent women from receiving adequate asthma care[40].

Asthma with comorbid anxiety is more prevalent in women than men[42,43]. As anxiety and stress can lead to HCPs taking patients' symptoms less seriously[40], it is possible that people with comorbid anxiety (women in particular) may be more likely to be misdiagnosed and/or receive sub-optimal asthma management[44]. In a 2006 study of patients with chronic obstructive pulmonary disease (COPD), a hypothetical case study was given to primary care physicians (PCPs), with half told the patient was a woman, and half told the same patient was a man. Results showed that COPD was more likely to be diagnosed in men than women, although this gender bias no longer appeared once the physicians were shown the patients' spirometry results[45]. It is possible that assumptions that women are less likely to smoke and more likely to manifest anxiety as respiratory complaints may have played a role.

Spirometry is a vital tool to help confirm an asthma diagnosis but is under-utilized in diagnosing asthma in primary care[10,46]; this has been exacerbated by infection-control precautions during the COVID-19 pandemic. Under-utilization of spirometry may be more predominant in women: a recent study in patients ≥66 years old with asthma, reported that women experienced significantly lower rates of spirometry than men[31]. The reasons for this are unclear, but the authors suggest it could be related to either provider and/or patient behaviors. Nevertheless, the study highlights the importance of basing asthma diagnoses on objective measures like spirometry, peak flow, and fractional exhaled nitric oxide (FeNO) tests, as women in the study also had higher rates of Emergency Department (ED) visits than men. Recent studies of spirometry data from transgender and gender non-binary patients have also demonstrated that, although spirometry reference values should be based on birth sex and not gender[47], until very recently, there has been a lack of guidance and hence inconsistent use of male and female reference ranges[48]. HCPs are often unsure whether reference ranges for birth sex or gender should be used, especially if patients feel discriminated against if birth sex is used[49]. This uncertainty may result in systemic or unconscious provider biases[48] and may lead to misdiagnosis and inappropriate treatment[50].

The gender of the HCP may also influence disease management. In a study of women general practice nurses, the nurses provided significantly more comprehensive information to women but discussed disease management more with men[51]. Furthermore, a 2020 study showed that female HCPs consulting with male patients discussed preventative interventions and lifestyle modification more often than any other patient–HCP gender combination[52]. This could be significant as it is probable that asthma educators are more likely to be women than men (as frontline HCPs are more likely to be women).

Author guidance:

- Be aware of implicit gender bias, and the impact this has on asthma diagnosis, time to diagnosis, choice and interpretation of tests, and management. Gender bias training and self-assessment tools are recommended to gain these insights. HCPs can assess their gender bias using the Harvard University self-assessment tool[53].
- Eliminating gender bias should help in treating patients as individuals. Health behavior concerns should be addressed equally in men and women; for example, although more women than men may be physically inactive, it is important to still ask men about their physical activity as well as women.
- Be aware of the importance of spirometry and its utilization to avoid both under- and over-treatment of asthma in men and women. Bronchial provocation (e.g., with methacholine), may also be used if a diagnosis cannot be reached[10].
- As sex is one of the predictive criteria for spirometry, consider what reference value ranges should be used for transgender patients. The 2019 American Thoracic Society and European Respiratory Society guidelines specify that patients should be informed that "birth sex and not gender is the determinant of predicted lung size" and using non-birth sex to calculate predicted spirometry values may lead to misdiagnosis and inappropriate treatment[47].

HCP–PATIENT RELATIONSHIP

Good HCP–patient communication is vital, and time spent with patients exploring their concerns, encouraging health behavior changes, and supporting self-management can improve medication adherence and asthma control[11]. Motivational communication is a form of patient-centered behavior-change counseling that focuses on enhancing internal motivation to engage in appropriate self-management behaviors[11,12,54]. There is evidence that the impact of motivational communication can depend on the gender of the patient and of the HCP[51].

The GINA 2022 report recommends that patients' own healthcare goals and treatment preferences are incorporated into their asthma management plan[10]. However, it is important to recognize that women and men may have different healthcare goals. A recent study reported that men were more likely than women to focus on disease-specific goals (e.g., asthma control and medication reduction) rather than function-related (e.g., social, emotional) or knowledge-related (e.g., asthma education) goals. Better asthma control was achieved when patients (regardless of sex/gender) focused on disease-specific goals[55].

Author guidance:

- Consider undertaking evidence-based training on motivational communication (Fig. 2)[12]. As the impact of motivational communication can depend on the gender of the patient and the HCP[51], training undertaken should try to address this discrepancy.
- Prioritize spending time with patients at the start of the relationship, as this can save time spent in the long run[11]. Specialist asthma educators, pharmacists, school nurses and other HCPs can also support PCPs in educating/supporting patients with asthma[56,57].
- Perform regular asthma reviews with all patients; discuss the patient's own healthcare goals and encourage them to focus on disease-specific goals.
- Implement the GINA cycle of care for all patients[10].

MANAGEMENT OF ASTHMA DURING PREGNANCY

Pregnancy affects asthma control in many women; approximately one-third of women report symptom worsening, one-third report symptom improvement, and one-third report no noticeable difference[10]. Poor maternal asthma control is associated with adverse outcomes, including increased risk of preterm birth, low birthweight, congenital malformations, perinatal death, and risk of childhood asthma[58–60]. In addition, a small reduction in the mother's oxygen levels (e.g., during an asthma exacerbation) can result in severe, life-threatening fetal hypoxia[61]. It is, therefore, vital that pregnant women (and women who are thinking of becoming pregnant) are educated on taking their asthma medications as prescribed and have a plan for managing exacerbations[62].

However, understandably, many women report being apprehensive about using asthma medication during pregnancy over concerns of teratogenicity, meaning that adherence to medications may decrease[63]. While the safety of most asthma

Table 1. Differential diagnoses of asthma in men and women.

More common in women	More common in men
Obesity[42,43]	COPD[43] [a]
Dysfunctional breathing, including vocal cord dysfunction and exercise-induced laryngeal obstruction (EILO)[69,70]	Lung cancer[71] [a]
Anxiety[43]	Idiopathic pulmonary fibrosis[72]
Bronchiectasis[73]	Heart failure[74]
Gastro-esophageal reflux[42,43]	Tuberculosis[75]
Upper airway cough syndrome[76]	
Pulmonary embolism[77]	
Systemic sclerosis-associated interstitial lung disease[78]	

COPD chronic obstructive pulmonary disease.
[a]COPD and lung cancer are generally higher in men globally, although incidence appears to be increasing in women, possibly due to increased tobacco use by women[71,81], and increased susceptibility to nicotine[20].

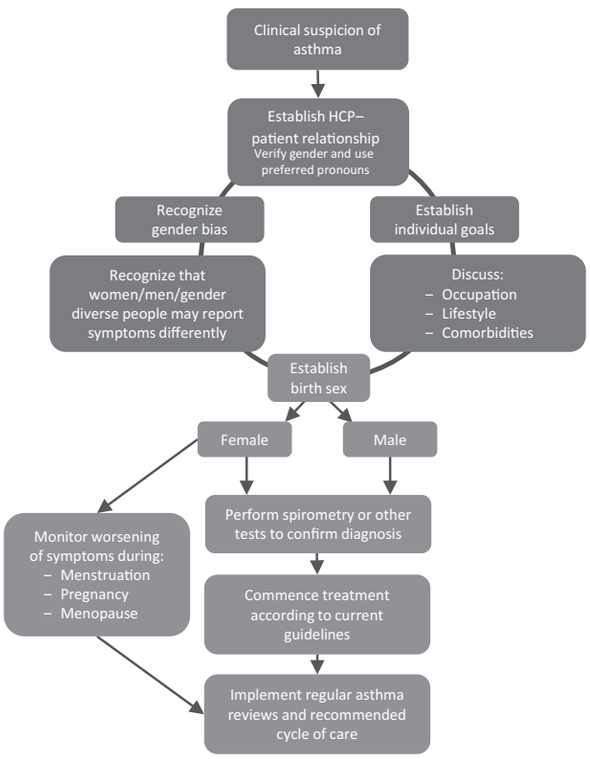

Fig. 3 Considerations of sex and gender differences in patient asthma management. HCP healthcare professional.

medications (e.g., ICS, SABAs, long-acting beta-agonists, leukotriene receptor antagonists, OCS, and biologics) has not been unequivocally proven in pregnancy, they have now been used successfully for decades. Overall, evidence indicates asthma medications are safe in pregnancy, and their use is justified, as the benefits of good symptom control markedly outweigh the potential risks to mother and baby[10,64,65].

Managing asthma symptoms during labor and delivery is also important, and guidelines advise women to continue with their usual asthma medications during this time[10]. Asthma symptoms occur in ~10% of deliveries[61], and a cesarean section may be required if an acute exacerbation occurs[66]. Neonatal hypoglycemia is also a risk, especially if the woman takes high doses of beta-agonists in the 48 h before birth or if the baby is premature[10]. Oxytocin is the preferred drug to induce labor where necessary[67]. However, although this is a rare event, there is evidence from a small number of case studies that oxytocin can cause anaphylaxis in women with asthma[68].

Author guidance:

- Inform pregnant patients of the detrimental effects of poorly controlled maternal asthma for their baby, both during pregnancy and after.
- Validate concerns using motivational communication and encourage pregnant patients to keep taking their asthma medication(s) as usual. The benefits of good symptom control outweigh the risks.
- As asthma symptoms may worsen or improve during pregnancy, instruct pregnant women on how to adjust their medication(s) appropriately and have an action plan for the management of exacerbations during pregnancy and labor.
- Inform pregnant women that although exacerbations during labor are rare, a cesarean section may be required in some instances if an exacerbation occurs[66].
- Aspects of pregnancy can mimic asthma symptoms (e.g., breathlessness). Understanding differential diagnosis and how to assess it (e.g. using spirometry[67]), could be useful when treating pregnant women with asthma.

DIFFERENTIAL DIAGNOSES

There may be difficulties in differentiating between symptoms caused by asthma and symptoms caused by other respiratory conditions (Table 1[20,42,43,69–79]). For example, asthma and COPD share common features which make differentiating them complicated, especially in older adults and smokers[80]. In developed countries, the prevalence of COPD in men and women is similar[81]. However, potentially due to HCP implicit bias and lack of spirometry use, women are more likely to receive a diagnosis of asthma rather than COPD[45,82]. Additionally, because anxiety disorders (e.g., panic disorders, which may be associated with hyperventilation and dysfunctional breathing) and obesity are more commonly diagnosed in women than men[42,43,69], women who report respiratory symptoms may have their symptoms attributed to anxiety or obesity, rather than taken seriously and investigated further.

Author guidance:

- Determine whether symptoms are due to asthma or another condition and assess the severity of symptoms in all patients by using objective tests such as spirometry.
- Be cautious about inferring anxiety disorders or obesity as a cause of symptoms based on the patient's sex or gender.

COMORBIDITIES

Comorbidities are associated with poor asthma outcomes[43]. Compared with men, women with asthma are more likely to have comorbidities, including obesity, osteoporosis, anxiety, and depression[43]. In addition, regular or frequent intake of OCS (and possibly high doses of ICS) to manage asthma symptoms increases the risk of developing side effects such as osteoporosis and cataracts[83]. As women are more likely than men to be prescribed OCS to manage their asthma symptoms[84] (possibly because women report more severe symptoms than men[4]), they may be more at risk of these side effects. However, it is worth noting that corticosteroid use increases the risk of these comorbidities (including osteoporosis) in men as well as

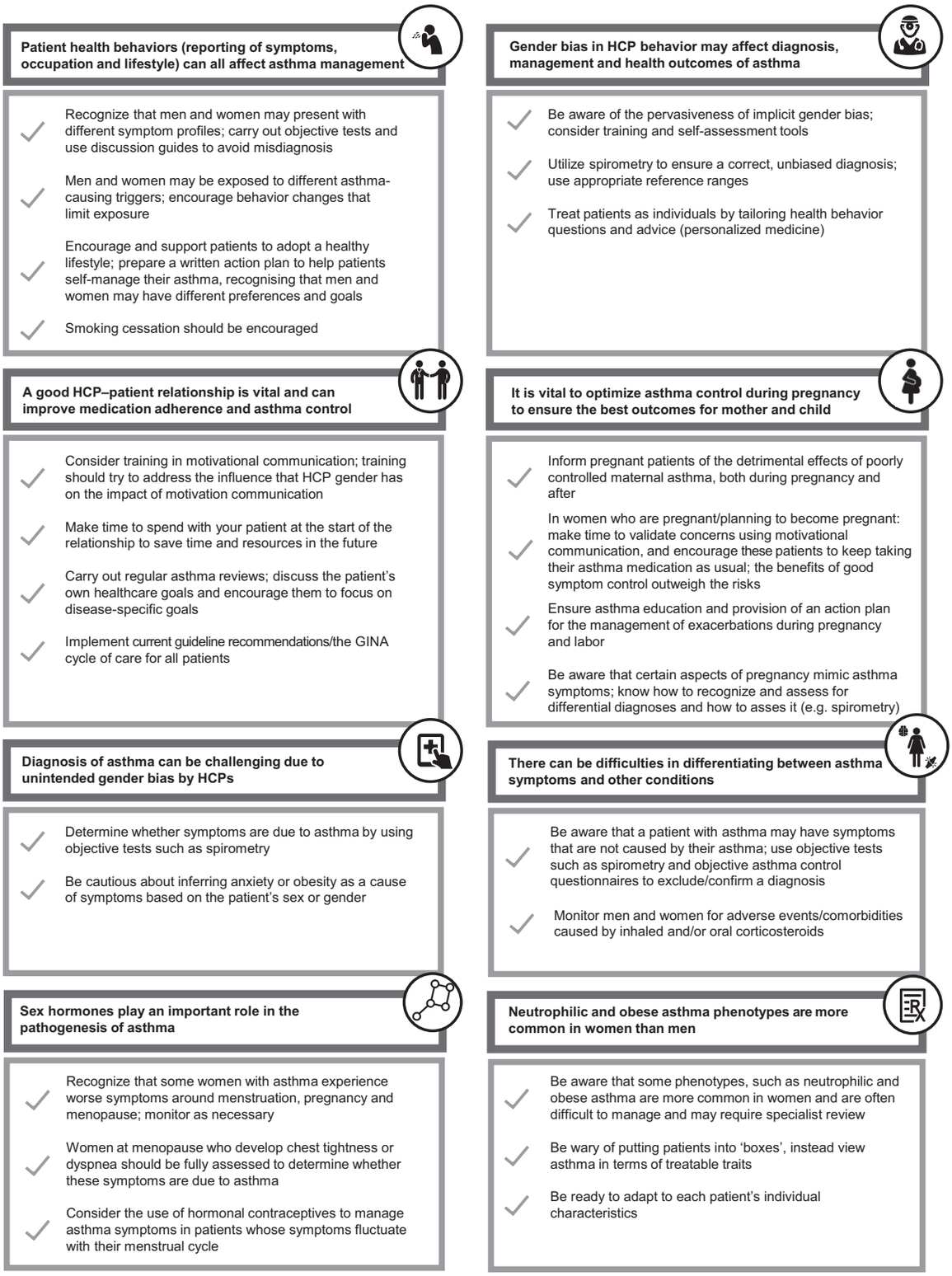

Fig. 4 Summary: Suggested actions to minimize the impact of sex and gender differences in asthma diagnosis and management. GINA Global Initiative for Asthma, HCP healthcare professional.

women[85]. Therefore, identifying patients who overuse corticosteroids is crucial for minimizing steroid-related comorbidities[86].

Author guidance:

- Be aware that not all symptoms that occur in someone with asthma are due to their asthma. Careful discussions with the patient and objective tests to explore the distinguishing

characteristics may be needed to avoid over-treatment with SABAs.
- Monitor both men and women for adverse events and comorbidities, including osteoporosis, particularly when using OCS as part of their asthma management regimen.

SEX HORMONES

Some women with asthma find that their symptoms worsen during certain phases in their menstrual cycle, during pregnancy, and at menopause[10,87,88]. Menopause is also associated with an increased risk of new-onset asthma[89]. Certain hormonal contraceptives have been shown to improve asthma symptoms and decrease the risk of asthma in pre-menopausal women[90]. It is interesting to note that, while estrogen and progesterone are involved in asthma pathogenesis, testosterone may protect against inflammatory processes that cause asthma[7]. However, there is a paucity of research into whether testosterone replacement therapy has beneficial effects on asthma, or if low testosterone (e.g., during andropause) affects asthma in men[91].

Author guidance:

- Recognize that some women with asthma may experience worse symptoms around menstruation, pregnancy and menopause.
- Hormonal contraceptives have the potential to improve asthma control in women whose symptoms fluctuate with their menstrual cycle.
- Fully assess women during pregnancy and at menopause who develop chest tightness or dyspnea to determine whether these symptoms are due to new-onset asthma, poor adherence to current asthma medication or other factors.

SEX/GENDER-SPECIFIC PHENOTYPES

Neutrophilic, obese asthma is a distinct phenotype that is more common in women than men and is often difficult to manage[92,93]. Women with neutrophilic, obese asthma tend to have lower lung function and a poor response to corticosteroids compared with non-obese women; this is not the case with men who have this phenotype[93,94]. Women may be more likely to have neutrophilia than men due to body composition. Women tend to have more subcutaneous than abdominal adipose fat, which secretes more leptin (a pro-inflammatory mediator that recruits neutrophils to the airways[95]), leading to increased neutrophilic inflammation[96]. Identifying a patient's phenotype is useful when ascertaining the most effective medication to prescribe. More recently, 'treatable traits' have been proposed for the management of complex airway diseases. These are phenotypic or endotypic characteristics that are clinically relevant, measurable, and treatable[97].

Author guidance:

- Be wary of putting patients into 'boxes', and view asthma in terms of 'treatable traits' for which there are evidence-based interventions. With personalized medicine in mind, be adaptable to each patient's individual characteristics.

DISCUSSION AND CONCLUSION

Sex and gender can affect patient health behaviors, and implicit gender bias by HCPs is widespread and may affect diagnosis, management, and health outcomes[38]. Our suggestions should support HCPs to provide personalized asthma care for all patients, regardless of sex or gender. Figure 3 is a simple algorithm for navigating the considerations surrounding sex and gender differences when diagnosing and managing asthma. Figure 4 provides suggestions for minimizing the impact of sex and gender differences in asthma diagnosis and management.

There are now many gender terms that people can use for self-identification. In everyday practice, HCPs will increasingly start to see patients with complex gender identities—so, although it is important to keep sex/gender differences in mind while diagnosing/managing asthma, it is crucial that HCPs treat patients as individuals and strive to provide personalized asthma care for all patients, regardless of sex or gender.

In addition, good collaboration must exist between all HCPs involved in the management of each patient (PCP, pneumologist, gynecologist etc.). Further research would allow HCPs to better account for sex/gender in diagnosing and treating their patients with asthma. Urgent research is needed to investigate the links between hormone changes and asthma in women and men, and the effects of testosterone. To this end, there is a need for greater consideration of sex and gender in the design and analysis of clinical trials. Clarity regarding the use and definition of 'male/female' and 'women/men' is also necessary and would be a good starting point. Ultimately, knowledge of the causes of sex and gender disparities in asthma diagnosis and management should be a high priority for new research on how to increase gender equity and improve quality in clinical practice. In view of the evidence that sex- and gender-related differences and biases can significantly and adversely impact diagnosis and management if not recognized, it is concerning that these differences are largely not taught during HCP training, including in curricula, or discussed in guidance followed by HCPs[10,98]. It is, therefore, our opinion, that updated guidance and resources are urgently needed to help HCPs minimize the impact that sex and gender have on asthma diagnosis and management. For individualized asthma management to become part of normal HCP practice, it is essential that a new approach to asthma research, diagnosis, and management is taken, one that considers sex and gender, while treating the patient as an individual.

DATA AVAILABILITY

This is a narrative review manuscript and does not report original research/data; thus, data sharing is not applicable.

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L.P.B.: made a substantial contribution to the initial concept of this review article, critically reviewed the intellectual content during the development process, and approved the final version to be published; K.L.L.: made a substantial contribution to the initial concept of this review article, critically reviewed the intellectual content during the development process, and approved the final version to be published; C.R.S.: made a substantial contribution to the initial concept of this review article, critically reviewed the intellectual content during the development process, and approved the final version to be published; A.K.: made a substantial contribution to the initial concept of this review article, critically reviewed the intellectual content during the development process, and approved the final version to be published; D.S.: made a substantial contribution to the initial concept of this review article, critically reviewed the intellectual content during the development process, and approved the final version to be published; C.R.J.: made a substantial contribution to the initial concept of this review article, critically reviewed the intellectual content during the development process, and approved the final version to be published.

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1. Biedermann T et al. J Allergy Clin Immunol. 2019;143:1058–66.
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ORION PHARMA

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C **Bufomix Easyhaler «Orion»** Adrenergikum + kortikosteroid. ATC-nr.: R03A K07

INHALASJONSPULVER 80 mikrogram/4,5 mikrogram, 160 mikrogram/4,5 mikrogram og 320 mikrogram/9 mikrogram: Hver avgitte dose inneh.: Budesonid 80 mikrogram, resp. 160 mikrogram og 320 mikrogram, formoterolfumaratdihydrat 4,5 mikrogram, resp. 4,5 mikrogram og 9 mikrogram, laktose. **Indikasjoner: 80 mikrogram/4,5 mikrogram:** Astma: Voksne, ungdom og barn ≥6 år: Regelmessig behandling ved behov for kombinasjon av langtidsvirkende β_2-reseptoragonist og inhalasjonskortikosteroid: For pasienter hvor inhalasjonskortikosteroid og korttidsvirkende β_2-reseptoragonister ved behov ikke gir tilstrekkelig kontroll av sykdommen, samt pasienter hvor inhalasjonskortikosteroid kombinert med langtidsvirkende β_2-reseptoragonister allerede gir tilstrekkelig kontroll av sykdommen. Ikke egnet til bruk ved alvorlig astma. **160 mikrogram/4,5 mikrogram og 320 mikrogram/9 mikrogram:** Astma: Voksne og ungdom ≥12 år: Regelmessig behandling ved behov for kombinasjon av langtidsvirkende β_2-reseptoragonist og inhalasjonskortikosteroid: For pasienter hvor inhalasjonskortikosteroid og korttidsvirkende β_2-reseptoragonister ved behov ikke gir tilstrekkelig kontroll av sykdommen, samt pasienter hvor inhalasjonskortikosteroid kombinert med langtidsvirkende β_2-reseptoragonister allerede gir tilstrekkelig kontroll av sykdommen. Kronisk obstruktiv lungesykdom (kols): Voksne ≥18 år: Symptomatisk behandling av kols-pasienter med FEV_1 (forsert ekspiratorisk volum i 1 sekund) <70% av forventet normalverdi (postbronkodilatator) og en eksaserbasjonshistorikk på tross av regelmessig bronkodilaterende behandling. **Dosering:** Astma: Ikke beregnet for initialbehandling ved astma. Behandlingen individualiseres og tilpasses sykdommens alvorlighetsgrad, både ved behandlingsstart og når vedlikeholdsdosen justeres. Ved behov for behandling i tillegg til kombinasjonsinhalatoren, bør passende dose av β_2-reseptoragonist og/eller kortikosteroid forskrives i separat inhalator. Dosen bør titreres til laveste dose som gir symptomkontroll. Pasienten bør følges jevnlig opp av lege/helsepersonell slik at dosen forblir optimal. Når langtids symptomkontroll er oppnådd med laveste anbefalte dose, kan inhalasjonskortikosteroid forsøksvis gis alene. **Vedlikeholdsbehandling:** Brukes regelmessig, med en separat, hurtigvirkende bronkodilatator som akuttmedisin. Pasienten bør rådes til å ha separat hurtigvirkende bronkodilatator tilgjengelig for akuttbruk til enhver tid. Vanligvis oppnås symptomkontroll med dosering 2 ganger daglig. Ved titrering til laveste effektive dose, er det mulig å forsøke dosering 1 gang daglig, når legen vurderer at en langtidsvirkende bronkodilatator i kombinasjon med et inhalasjonskortikosteroid er nødvendig for å opprettholde kontroll. Økt bruk av separat hurtigvirkende bronkodilatator tyder på forverring av underliggende sykdom og krever ny vurdering av behandlingen. **80 mikrogram/4,5 mikrogram:** Voksne ≥18 år: 1-2 inhalasjoner 2 ganger daglig. Enkelte kan ha behov for opptil maks. 4 inhalasjoner 2 ganger daglig. Ungdom 12-17 år: 1-2 inhalasjoner 2 ganger daglig. Barn ≥6 år: 2 inhalasjoner 2 ganger daglig. Barn <6 år: Anbefales ikke. **160 mikrogram/4,5 mikrogram:** Voksne ≥18 år: 1-2 inhalasjoner 2 ganger daglig. Enkelte kan ha behov for opptil maks. 4 inhalasjoner 2 ganger daglig. Ungdom 12-17 år: 1-2 inhalasjoner 2 ganger daglig. Barn ≥6 år: Se 80 mikrogram/4,5 mikrogram. Barn <6 år: Anbefales ikke. **320 mikrogram/9 mikrogram:** Skal kun brukes til vedlikeholdsbehandling. Voksne ≥18 år: 1 inhalasjon 2 ganger daglig. Enkelte kan ha behov for opptil maks. 2 inhalasjoner 2 ganger daglig. Ungdom 12-17 år: 1 inhalasjon 2 ganger daglig. Barn ≥6 år: Se 80 mikrogram/4,5 mikrogram. Barn <6 år: Anbefales ikke. **Vedlikeholds- og anfallskuperende behandling:** Daglig vedlikeholdsdose og i tillegg ved behov. Preparatet bør være tilgjengelig for akuttbruk. For pasienter som tar Bufomix Easyhaler som symptombehandling skal lege og pasient diskutere forebyggende behandling med Bufomix Easyhaler mot allergen- eller anstrengelsesutløst bronkokonstriksjon. Anbefalt bruk skal ta hensyn til hyppigheten av behovet. Ved hyppig behov for bronkodilatasjon uten korresponderende behov for en økt dose av inhalerte kortikosteroider bør annen symptombehandling brukes. Vedlikeholds- og anfallskuperende behandling bør vurderes spesielt ved utilfredsstillende astmakontroll og hyppig behov for anfallskuperende behandling, og når tidligere astmaeksaserbasjoner har krevd medisinsk behandling. Tett oppfølging av doserelaterte bivirkninger er nødvendig hos pasienter som tar et høyt antall inhalasjoner ved behov. **80 mikrogram/4,5 mikrogram:** Voksne og ungdom ≥12 år: Anbefalt vedlikeholdsdose er 2 inhalasjoner daglig, enten 1 morgen og 1 kveld eller 2 inhalasjoner enten morgen eller kveld. Ved symptomer kan 1 tilleggsinhalasjon tas ved behov. Dersom symptomene vedvarer etter noen minutter, bør det tas 1 tilleggsinhalasjon. Det bør ikke tas >6 inhalasjoner ved ett enkelt doseringstilfelle. Det er vanligvis ikke nødvendig med >8 inhalasjoner daglig. Det kan likevel brukes inntil 12 inhalasjoner daglig i en begrenset periode. Ved bruk av >8 inhalasjoner daglig bør lege kontaktes. Pasienten bør undersøkes og vedlikeholdsdosen revurderes. Barn <12 år: Anbefales ikke. **160 mikrogram/4,5 mikrogram:** Voksne og ungdom ≥12 år: Anbefalt vedlikeholdsdose er 2 inhalasjoner daglig, enten 1 morgen og 1 kveld eller 2 inhalasjoner enten morgen eller kveld. For noen kan en vedlikeholdsdose på 2 inhalasjoner 2 ganger daglig være nødvendig. Ved symptomer kan 1 tilleggsinhalasjon tas ved behov. Dersom symptomene vedvarer etter noen minutter, bør det tas 1 tilleggsinhalasjon. Det bør ikke tas >6 inhalasjoner ved ett enkelt doseringstilfelle. Det er vanligvis ikke nødvendig med >8 inhalasjoner daglig. Det kan likevel brukes inntil 12 inhalasjoner daglig i en begrenset periode. Ved bruk av >8 inhalasjoner daglig bør lege kontaktes. Pasienten bør undersøkes og vedlikeholdsdosen revurderes. Barn <12 år: Anbefales ikke. **Kols: 160 mikrogram/4,5 mikrogram:** Voksne: 2 inhalasjoner 2 ganger daglig. **320 mikrogram/9 mikrogram:** Voksne: 1 inhalasjon 2 ganger daglig. **Spesielle pasientgrupper:** Nedsatt lever-/nyrefunksjon: Data mangler. Økt eksponering av budesonid og formoterol kan forventes ved alvorlig levercirrhose. Barn <6 år: Anbefales ikke. Eldre: Dosejustering ikke nødvendig. **Administrering:** Til inhalasjon. For bruksanvisning, se SPC og pakningsvedlegg. For å minske risiko for soppinfeksjon i munn/svelg bør munnen skylles med vann etter hver vedlikeholdsdosering. Ved soppinfeksjon i munn/svelg, bør munnen skylles med vann også etter anfallskuperende behandling. Pasienten skal inhalere hurtig og kraftig, og ikke puste ut i apparatet. **Kontraindikasjoner:** Overfølsomhet for innholdsstoffene. **Forsiktighetsregler:** Dosen bør trappes gradvis ned ved seponering, og behandling bør ikke avsluttes brått. Fullstendig seponering av inhalerte kortikosteroider bør unngås, med mindre det er midlertidig behov for å bekrefte diagnosen astma. Dersom pasienten mener behandlingen ikke er effektiv eller bruker flere doser enn høyeste anbefalte dose, skal lege oppsøkes. Plutselig og tydelig forverring av astma eller kols er potensielt livstruende, og pasienten trenger umiddelbar medisinsk utredning. Det skal vurderes om det er behov for å øke behandling med kortikosteroider, f.eks. orale kortikosteroider, eller antibiotikabehandling ved infeksjon. Pasienten bør minnes på å ta vedlikeholdsdosen som forskrevet, også ved symptomfrihet. Når astmasymptomene er under kontroll bør det vurderes en gradvis nedtrapping av dosen. Det er viktig med regelmessig vurdering ved nedtrapping. Alvorlige astmarelaterte bivirkninger og eksaserbasjoner kan oppstå. Behandling skal ikke initieres under en eksaserbasjon, eller ved signifikant eller akutt forverring av astma. Pasienten skal rådes til å fortsette behandlingen, men kontakte lege ved ukontrollerte eller forverrede astmasymptomer. Studiedata mangler for kols-pasienter med FEV_1 >50% av forventet normalverdi pre-bronkodilatator og med FEV_1 <70% av forventet normalverdi post-bronkodilatator. Paradoksal bronkospasme: Kan oppstå og gi umiddelbar økning i pipende/hvesende pust og andpustenhet. Preparatet skal da seponeres umiddelbart, pasienten vurderes, og alternativ behandling startes om nødvendig. Paradoksal bronkospasme responderer på hurtigvirkende inhalert bronkodilatator og bør behandles umiddelbart. Systemiske effekter: Systemiske effekter av inhalasjonskortikosteroider kan forekomme, spesielt ved høye doser over lengre tid. Effektene er trolig avhengige av dose, eksponeringstid, samtidig og tidligere steroideksponering og individuell følsomhet. Synsforstyrrelser er sett ved bruk av systemiske og topikale kortikosteroider. Ved synsforstyrrelser, inkl. tåkesyn, skal pasienten vurderes for henvisning til øyelege for vurdering av årsaker, inkl. grå/grønn stær eller sentral serøs chorioretinopati (CSCR), som er rapportert ved bruk. Potensielle effekter på bentetthet bør vurderes, spesielt hos pasienter med samtidige risikofaktorer for osteoporose, og som bruker høye doser over lengre perioder. Langtidsbruk av inhalert budesonid med gjennomsnittlige daglige doser på 400 mikrogram til barn og 800 mikrogram til voksne, har ikke vist signifikant effekt på benmineraltettheten. Ved mistanke om nedsatt binyrebarkfunksjon pga. tidligere systemisk steroidbehandling, bør forsiktighet utvises ved behandlingsstart. Inhalert budesonid vil normalt minimere behovet for orale steroider, men ved overføring fra orale steroider er det risiko for vedvarende redusert binyrerespons. Etter avsluttet behandling med orale steroider, kan pasienter med oral steroidavhengighet som overføres til inhalert budesonid, ha risiko for nedsatt binyrebarkfunksjon i lengre tid. I slike tilfeller bør HPA-aksens funksjon overvåkes jevnlig. Langvarig behandling med høye doser inhalasjonskortikosteroider, spesielt doser høyere enn anbefalt, kan også gi klinisk signifikant binyrebarkssuppresjon. Ytterligere systemisk kortikosteroiddekning bør derfor vurderes i perioder med stress, som ved alvorlige infeksjoner eller elektiv kirurgi. Rask reduksjon av steroiddosen kan indusere akutt adrenerg krise. Behandling med supplerende systemiske steroider eller inhalert budesonid bør ikke avbrytes brått. Overgang fra oral behandling vil gi en generelt lavere systemisk steroidvirkning, noe som kan gi allergiske eller artrittiske symptomer som rhinitt, eksem og muskel-/leddsmerter. Spesifikk behandling bør innledes ved disse lidelsene. En generell utilstrekkelig glukokortikoideffekt bør mistenkes ved symptomer som tretthet, hodepine, kvalme og brekninger. Det kan da være nødvendig med midlertidig økning av den orale glukokortikoiddosen. Pneumoni ved kols: Økt forekomst av pneumoni, inkl. pneumoni som krever sykehusinnleggelse, er sett hos kols-pasienter som bruker inhalasjonskortikosteroider. Vær oppmerksom på mulig utvikling av pneumoni hos kols-pasienter, da kliniske tegn kan ligne symptomer på kols-eksaserbasjoner. Risikofaktorer inkluderer røyking, høy alder, lav BMI og alvorlig kols. Annet: Forsiktighet bør utvises ved tyreotoksikose, feokromocytom, diabetes mellitus, ubehandlet hypokalemi, hypertrofisk obstruktiv kardiomyopati, idiopatisk subvalvulær aortastenose, alvorlig hypertensjon, aneurisme eller andre alvorlige hjerte-karlidelser som iskemisk hjertesykdom, takyarytmier eller alvorlig hjertesvikt. Formoterol kan indusere forlenget QT_C-intervall. Forsiktighet bør utvises ved forlenget QT_C-intervall. Behov for inhalasjonskortikosteroid, samt dose, bør revurderes hos pasienter med aktiv eller sovende lungetuberkulose, sopp- og virusinfeksjon i luftveiene. Potensielt alvorlig hypokalemi kan oppstå ved høye doser β_2-reseptoragonister. Samtidig behandling med legemidler som kan indusere hypokalemi eller potensere hypokalemisk effekt kan forsterke den mulige hypokalemiske effekten. Spesiell forsiktighet bør utvises ved ustabil astma ved varierende bruk av bronkodilatator som akuttmedisin, ved akutt alvorlig astma da tilhørende risiko kan forsterkes pga. hypoksi, og ved andre tilstander der sannsynlighet for hypokalemi er økt. I slike tilfeller bør serumkaliumnivået følges. Ekstra blodsukkermåling bør vurderes hos diabetikere. Candidainfeksjon i orofarynks skyldes legemiddeldeponering. Orofaryngeal candidainfeksjon responderer ofte på lokal antifungal behandling uten at det er nødvendig å seponere inhalasjonskortikosteroidet. Inneholder små mengder melkeprotein som kan forårsake allergiske reaksjoner. Barn og ungdom: Ved langstidsbehandling med inhalasjonskortikosteroider til barn anbefales det at høyden måles regelmessig. Ved langsom vekst bør behandlingen gjennomgås mtp. dosereduksjon til laveste, effektive dose. Fordel av kortikosteroidbehandling skal vurderes nøye opp mot risiko for veksthemming. Henvisning til pediatrisk lungespesialist bør også vurderes. Langtidsdata tyder på at de fleste barn og unge som behandles med budesonid til inhalasjon til slutt når sin normalhøyde som voksne. Det er sett en liten, men forbigående, reduksjon i vekst (ca. 1 cm). Dette oppstår vanligvis i løpet av første behandlingsår. **Interaksjoner:** For utfyllende informasjon om relevante interaksjoner, bruk interaksjonsanalyse. Potente CYP3A-hemmere vil trolig gi en betydelig økning i plasmanivå av budesonid, og samtidig bruk bør unngås. Dersom dette ikke er mulig, bør tidsintervallet mellom administrering av hemmer og budesonid være lengst mulig. Vedlikeholdsbehandling og anfallskuperende behandling anbefales ikke ved bruk av CYP3A-hemmere. Samtidig behandling med CYP3A-hemmere forventes å øke risiko for systemiske bivirkninger. Kombinasjon bør unngås med mindre fordel oppveier økt risiko for systemiske bivirkninger av kortikosteroider. I slike tilfeller skal pasienten overvåkes for systemiske kortikosteroideffekter. Betablokkere (inkl. øyedråper) kan svekke eller hemme effekten av formoterol, og bør derfor ikke gis samtidig dersom det ikke er helt nødvendig. Samtidig behandling med kinidin, disopyramid, prokainamid, fentiaziner, antihistaminer (terfenadin) og TCA kan forlenge QT_C-intervallet og øke risiko for ventrikulære arytmier. Levodopa, levotyroksin, oksytocin og alkohol kan nedsette kardial toleranse for β_2-reseptoragonister. Samtidig behandling med MAO-hemmere, inkl. legemidler med tilsvarende egenskaper, kan utløse hypertensive reaksjoner. Forhøyet risiko for arytmier ved samtidig anestesibehandling med halogenerte hydrokarboner. Samtidig bruk av andre betaadrenerge eller antikolinerge legemidler kan ha mulig additiv bronkodilaterende effekt. Behandling med β_2-reseptoragonist kan gi hypokalemi, som kan forsterkes av samtidig behandling med xantin-derivater, kortikosteroider og diuretika. Hypokalemi kan øke risikoen for arytmier ved samtidig bruk av digitalisglykosider. **Graviditet, amming og fertilitet:** Graviditet: Bør kun brukes under graviditet når nytte oppveier potensiell risiko. Lavest effektive budesonoddose bør brukes. Dyrestudier viser at prenatal påvirkning av glukokortikoider øker risiko for intrauterin veksthemming, kardiovaskulær sykdom hos voksne og permanent endring i tetthet av glukokortikoide reseptorer, nevrotransmitteromsetning og atferd, ved eksponering under det teratogene doseringsintervallet. Amming: Det bør vurderes om fordelen for moren er større enn mulig risiko for barnet. Budesonid: Utskilles i morsmelk. Det forventes ingen effekter av budesonid hos diende barn der mor behandles med terapeutiske doser. Formoterol: Overgang i morsmelk er ukjent. Fertilitet: Formoterol kan gi noe redusert fertilitet hos hannrotte ved høy systemisk eksponering. **Bivirkninger:** Vanlige (≥1/100 til <1/10): Hjerte/kar: Palpitasjoner. Infeksiøse: Candidainfeksjoner i orofarynks, pneumoni (kols-pasienter). Luftveier: Mild irritasjon i halsen, hoste, heshet. Nevrologiske: Hodepine, tremor. Mindre vanlige (≥1/1000 til <1/100): Gastrointestinale: Kvalme. Hjerte/kar: Takykardi. Hud: Blåmerker. Muskel-skjelettsystemet: Muskelkramper. Nevrologiske: Svimmelhet. Psykiske: Aggresjon, psykomotorisk hyperaktivitet, angst, søvnforstyrrelser. Øye: Tåkesyn. Sjeldne (≥1/10 000 til <1/1000): Hjerte/kar: Hjertearytmier, f.eks. atrieflimmer, supraventrikulær takykardi, ekstrasystoler. Immunsystemet: Umiddelbare og forsinkede overfølsomhetsreaksjoner, f.eks. eksantem, urticaria, pruritus, dermatitt, angioødem og anafylaktisk reaksjon. Luftveier: Bronkospasme. Stoffskifte/ernæring: Hypokalemi. Svært sjeldne (<1/10 000): Endokrine: Cushings syndrom, binyresuppresjon, veksthemming, nedsatt benmineraltetthet. Hjerte/kar: Angina pectoris, forlenget QT_C-intervall, blodtrykksvariasjoner. Nevrologiske: Smaksforstyrrelser. Psykiske: Depresjon, atferdsrelaterte endringer (primært hos barn). Stoffskifte/ernæring: Hyperglykemi. Øye: Katarakt, glaukom. Ukjent frekvens: Behandling med β_2-reseptoragonister kan gi økt nivå av insulin, frie fettsyrer, glyserol og ketonlegemer i blodet. Økt mottakelighet for infeksjoner og nedsatt evne til å tilpasse seg stress kan også forekomme. **Overdosering/Forgiftning:** Symptomer: Formoterol: Tremor, hodepine, palpitasjoner. Det er sett isolerte tilfeller av takykardi, hyperglykemi, hypokalemi, forlenget QT_C-intervall, arytmier, kvalme og oppkast. Budesonid: Ved kronisk bruk i høye doser kan systemeffekter som hyperkortisisme og binyrebarksuppresjon forekomme. Behandling: Støttende og symptomatisk behandling. Dersom behandlingen må seponeres pga. overdose med formoterol, skal behandling med passende inhalasjonskortikosteroid vurderes. Se Giftinformasjonens anbefalinger for formoterol R03A C13 og glukokortikoider H02A B på www.felleskatalogen.no. **Egenskaper:** For farmakologiske egenskaper, se pkt. 5 i preparatomtalene. **Pakninger og priser: 80 mikrogram/4,5 mikrogram:** 120 doser[2] kr 417,40 (trinnpris 268,60). 3 × 120 doser[2] kr 1179,80 (trinnpris 733,20). **160 mikrogram/4,5 mikrogram:** 120 doser[1] kr 417,40 (trinnpris 285,60). 3 × 120 doser[1] kr 1179,80 (trinnpris 784,30). **320 mikrogram/9 mikrogram:** 60 doser[1] kr 396,60 (trinnpris 280,40). 3 × 60 doser[1] kr 1079,40 (trinnpris 768,70). **Refusjon:** Refusjonsberettiget bruk: [1]Regelmessig behandling av bronkialastma når det er behov for en kombinasjon av langtidsvirkende beta-agonist og inhalasjonssteroid for pasienter hvor inhalasjonssteroid og korttidsvirkende $beta_2$-agonister ikke gir tilstrekkelig kontroll av sykdommen samt for pasienter hvor inhalasjonssteroid kombinert med langtidsvirkende $beta_2$ agonist allerede gir tilstrekkelig kontroll av sykdommen. Refusjon ytes kun til pasienter med moderat og alvorlig KOLS (FEV1 < 60% av forventet verdi). Refusjonskode:

ICPC		Vilkår nr
R95	Kronisk obstruktiv lungesykdom	90
R96	Astma	92

ICD		Vilkår nr
J44	Annen kronisk obstruktiv lungesykdom	90
J45	Astma	92

Vilkår: (90) Refusjon ytes kun til pasienter med etablert KOLS. - Diagnosen må være verifisert ved spirometri. - Hvis spirometri ikke kan gjennomføres, må årsaken journalføres. (92) Diagnosen astma må være verifisert ved hjelp av spirometri hos barn over 8 år og voksne. Hvis spirometri ikke kan gjennomføres, må årsaken journalføres.

[2]Regelmessig behandling av bronkialastma når det er behov for en kombinasjon av langtidsvirkende $beta_2$-agonist og inhalasjonssteroid: - for pasienter hvor inhalasjonssteroid og korttidsvirkende $beta_2$-agonist ikke gir tilstrekkelig kontroll av sykdommen - for pasienter hvor inhalasjonssteroid kombinert med langtidsvirkende $beta_2$-agonist allerede gir tilstrekkelig kontroll av sykdommen. Cystisk fibrose.

ICPC		Vilkår nr
R96	Astma	92
T99	Cystisk fibrose	-

ICD		Vilkår nr
E84	Cystisk fibrose	-
J45	Astma	92

Vilkår: (92) Diagnosen astma må være verifisert ved hjelp av spirometri hos barn over 8 år og voksne. Hvis spirometri ikke kan gjennomføres, må årsaken journalføres.

Behandlingen (2 ganger daglig i 5 dager) bør starte umiddelbart etter en positiv covid-19 test og ≤ 5 dager etter symptomdebut[1]

88%

Relativ risikoreduksjon for sykehusinnleggelse eller død vs. placebo i EPIC-HR studien[2*]

Referanser: 1. PAXLOVID SPC **2.** Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with covid-19. *N Engl J Med*. 2022;386(15):1397-1408.
*Hos pasienter som fikk behandling innen 5 dager etter symptomdebut, og som ikke fikk behandling med monoklonalt antistoff ved baseline, ble den absolutte risikoen for sykehusinnleggelse eller død redusert fra 6.4% til 0.78%, dvs med 5.62 prosentpoeng (95 % KI = -7.21, -4.03), p<0.001.

Indikasjon: PAXLOVID® er godkjent for behandling av covid-19 hos voksne som ikke har behov for supplerende oksygenbehandling, og som har økt risiko for å utvikle alvorlig covid-19 sykdom.[1]

Les mer om hvilke risikogrupper som anbefales Paxlovid® ved å skanne QR-koden.

▼ **Paxlovid relevant sikkerhetsinformasjon**:
Anbefalt dose er 300 mg nirmatrelvir (2 rosa tabletter) og 100 mg ritonavir (1 hvit tablett), som alle tas samtidig hver 12. time i 5 dager. Fullføring av 5-dagerskuren anbefales selv om pasienten må innlegges på sykehus pga. alvorlig/kritisk covid-19. Ved moderat nedsatt nyrefunksjon (eGFR ≥30-<60 ml/minutt), skal dosen nirmatrelvir reduseres til 150 mg (1 rosa tablett) hver 12. time i 5 dager. Både nirmatrelvir og ritonavir er CYP3A-substrater. Samtidig behandling med andre legemidler som metaboliseres via, hemmer eller induserer CYP3A4 kan føre til interaksjoner som potensielt kan gi alvorlige, livstruende eller fatale hendelser. **Det må derfor gjøres en fullstendig gjennomgang av pasientens legemidler, inkludert reseptfrie legemidler og kosttilskudd, og et interaksjons-søk før behandling med Paxlovid igangsettes.** Pasienter bør overvåkes for bivirkninger forbundet med de samtidig administrerte legemidlene. Paxlovid er kontraindisert ved alvorlig nedsatt leverfunksjon og ved alvorlig nedsatt nyrefunksjon (eGFR <30 ml/minutt). Tilfeller av toksisk epidermal nekrolyse og Stevens-Johnsons syndrom har blitt rapportert. Paxlovid tabletter skal kun forskrives på blå resept (blåreseptforskriften §4) til pasienter med bekreftet smitte av SARS-CoV-2, som har høyest risiko for å utvikle alvorlig sykdom. Følg faglige anbefalinger fra Helsedirektoratet. Pris kr 0,-. Pakningsstørrelse 20 stk. + 10 stk. (blister). Reseptgruppe: C.

Se preparatomtale (SPC) for fullstendig informasjon.

Pfizer

▼Paxlovid™
(nirmatrelvir 150 mg tabletter | ritonavir 100 mg tabletter)