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Helsedirektoratet

Allergifrisk 2015-2024

Handlingsprogram for astma, allergi og annen overfølsomhet

FORORD

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INNHOLD

INNLEDNING

Status

Strategien for forebygging og behandling av astma- og allergisykdommer 2008- 2012 har ikke nådd det overordnede målet om å redusere forekomsten av astma og allergi. Dagens datagrunnlag er imidlertid for dårlig til å si noe sikkert om utviklingen, og for dårlig til å si noe sikkert om effekten av tiltakene fram til 2012. Mangelen på gode data for forekomst, livskvalitet, og beskyttende og utløsende faktorer er også et uheldig utgangspunkt for en ny strategi. Å få på plass et betydelig bedre datagrunnlag bør derfor være sentralt i den kommende strategiperioden. Når det gjelder forebygging, har vi imidlertid oppnådd betydelige resultater. Det er gjennomført tiltak for å fjerne årsakene til veksten, og for å fjerne faktorer som gjør det krevende å leve med sykdommene. Det er økt samhandling mellom alle samfunnssektorer og mellom myndigheter, fagmiljøer og frivillig sektor. Et eksempel er veimyndighetenes tiltak for å redusere lokal luftforurensning fra utslipp fra kjøretøy. Samarbeid om inneklima skjer mellom alt fra byggetekniske fagmiljøer til lokale skoleeiere.

For å følge opp strategien for perioden 2008-2012 ble det tidlig i perioden etablert en egen koordineringsgruppe. I 2011 fikk de regionale helseforetakene i oppdrag å etablere tverrfaglige regionale kompetansemiljøer for astma- og allergisykdommer med rådgivning og kompetanseoverføring som hovedoppgaver. Etableringen skulle finne sted innen utgangen av sommeren 2013. Det er ulikt hvordan de fire helseregionene har løst oppgaven. Egen statusoversikt er levert HOD våren 2014. Et Kompetanseområde for allergologi ble opprettet i 2012.

I strategiperioden er det videre opprettet seks referansegrupper for å belyse og presentere forslag til flere tiltak innenfor astma, allergi- og overfølsomhetsområdet, som ledd i å oppfylle målene i strategiplanen. Disse referansegruppene har levert betydelige bidrag og kunnskapsgrunnlag innen områdene inneklima og uteluft, mat og kosmetikk, diagnostikk og behandling, forskning samt opplæring og rehabilitering. En egen gruppe har dessuten drøftet organisering og innhold i de regionale allergisentrene.

Koordineringsgruppen har fungert som styringsgruppe for arbeidet i referansegruppene. Astma- og Allergiforbundet (NAAF) er representert i samtlige grupper. I 2013 ble det avholdt to samlinger med alle ovennevnte grupper med henblikk på innspill til nytt AAO-program for 2015-2024. Samtlige grupper fikk i oppdrag å utarbeide et skriftlig grunnlag med forslag om tiltak for å snu utviklingen/økningen av astma, allergi og overfølsomhetsreaksjoner i Norge. Innspillene ligger til grunn for det foreliggende utkastet til nytt program.

Innenfor diagnostikk og behandling var målet i strategien for 2008-2012 en tydelig erkjennelse av behovet for tidlig og riktig diagnose, samt at opplæring av pasienter og pårørende må integreres i selve behandlingen. Den viktigste utfordringen for Norge ligger i de høye tallene vi har for astma og allergi. I den tidligere strategien vises det til en forekomst av astma på 20 prosent blant tiåringer i Oslo som hadde, eller hadde hatt, sykdommen (2004), 11 prosent hadde aktiv astma (Carlsen et. al). Samme studie viste at blant sekstenåringer i 2010 hadde 27 prosent hatt, eller hadde astma fortsatt. Blant disse 16 åringene hadde 13 prosent aktiv astma fortsatt. Den samme undersøkelsen viser at enda flere barn er sensibilisert for allergi. Resultatene ved tiårsalder viser positiv prikktest hos 27 prosent. Ved sekstenårs alder er dette økt til 45 prosent. Dette sammenfaller med WHOs prognose for allergisk sykdom som antyder at 50 prosent av befolkningen vil ha en eller annen allergisk manifestasjon i 2030, gitt at utviklingen fortsetter som nå.

Vi mangler i dag kunnskap innenfor de fire kjerneområdene; Forskning som bidrar til redusert byrde (forekomst og sykelighet) gjennom miljørettede helsefremmende og forebyggende tiltak, bedret diagnostikk og behandling, styrket og optimalisert samhandling i helsetjenestene og godt kunnskapsgrunnlag for offentlig rådgivning om astma, allergi og overfølsomhetssykdommer.

Ny kunnskap

Ny kunnskap viser at økningen i barneastma gir økt risiko for KOLS, spesielt hos gutter. Det er nylig også dokumentert at lav lungefunksjon tidlig i livet, øker risikoen for astma og KOLS senere i livet.

Nyere forskning tyder på at den økende forekomsten i pollenallergi kan bidra til vekst i forekomsten av allergiske reaksjoner på mat. Årsaken er at pollenallergi kan gi kryssreaksjoner mot visse frukter, grønnsaker og nøtter. Selv om forekomsten av pollenallergi er vanskelig å fastslå helt nøyaktig, må vi fastslå at forekomsten er relativ høy i Norge og at pollenallergi er den hyppigst forekommende allergien. Det er anslått at over 20% av befolkningen reagerer mot en eller flere typer pollen. (*Roald Bolle 2014*). Nyere kunnskap tyder også på at eksponering for fuktskader og muggsopp i inneklimaet ikke bare er knyttet til forverring av astma, men også til utvikling av sykdommen.

Innsatsen i strategiperioden har hatt et betydelig innslag av helsefremmende og sykdomsforebyggende grep. Effekten av denne typen tiltak tar lang tid å dokumentere, og det vil derfor ta tid før effekten kan leses av på redusert forekomst eller økt livskvalitet blant diagnostiserte. Tiltakene er også ofte komplekse og avhengige av politiske holdninger og beslutninger ute i samfunnet. Som eksempel på dette kan nevnes virkningene av nye kostråd og nye ammeråd som allerede er lansert i befolkningen, men som det tar tid å få folk til å slutte opp om. Det tar ofte lang tid å implementere og vurdere effekten av ny rådgivning på et område. Det samme gjelder utvikling av nye retningslinjer/guidelines.

SAMMENDRAG

Allergifrisk 2015-2024

Med betydelig bistand fra fagmiljøene og organisasjonene har Helsedirektoratet utarbeidet et forslag til program for perioden 2015 til 2024. Det overordnede målet for det nye programmet gir seg selv; å bidra til å redusere forekomst og sykelighet av astma, allergi og overfølsomhetsreaksjoner (AAO), og å redusere belastningen som dette innebærer både for enkeltindividet og for samfunnet. I programperioden skal og bør det altså bli betydelig lettere å leve med plager forårsaket av AAO. Programmet vil bidra til en kunnskaps- og samfunnsutvikling som reduserer AAO-sykdommer og som fremmer helse, miljø og bærekraft

Et paradigmeskifte

Den forrige strategiplanen og forebyggende tiltak/råd har til nå vært innrettet mot å unngå allergener. Dette «dogmet» har manglet solid evidens, og har heller ikke bremset eller reversert allergiepidemien. Å unngå allergener vil imidlertid fortsatt være en del av behandlingsmetodene for individuelle pasienter.

Bakgrunnen for at det nå anbefales et paradigmeskifte, er en foreløpig evaluering av det finske handlingsprogrammet, og nyere forskning med bakgrunn i «biodiversitetshypotesen». Erfaringene tyder på at det å gjenopprette og styrke toleransen for allergener, kan være nøkkelen til bedre immunbalanse på populasjonsnivå og bør være mer i fokus. Å forstå mekanismene bak immuntoleranse leder dessuten veien fra behandling til forebygging, allergi-helse og folkehelse generelt.

Anbefalingene til den generelle befolkningen har i høy grad manglet tilstrekkelig forankring i forskning. Det er fortsatt store kunnskapshull innenfor hele AAO-området – men vår vurdering er at det nå er sterkere dokumentasjon for en betydelig justering av befolkningsrådene.

Handlingsprogrammet Allergifrisk 2015-2024 er altså tuftet på en konsensus om at det er tid for å revurdere mye av synet på astma og allergi. I tillegg kommer at vi i Norge også vil måtte forholde oss til andre overfølsomhetsreaksjoner på en mer forpliktende måte. Først og fremst vil det gjelde ulike former for matintoleranse. Det er så langt ingen signaler som tyder på at utviklingen på dette området er i ferd med å snu. Bekymringen er stor både i fagmiljøene og i pasientorganisasjonene.

Programmet legger vekt på helsefremmende og forbyggende tiltak. Det vil være fokus på faktorer i det ytre miljø (uteluft og innemiljø) som påvirker astma og allergi, og som kan forårsake (andre) overfølsomhetsreaksjoner.

Informasjon, kunnskapsspredning og kompetansebygging

Å spre og dele kunnskap og stimulere til økt forskningsinnsats er sentrale søyler i programmet. Et sentralt tiltak er derfor å etablere og drive nettverk på tvers av de berørte departementene og direktoratene, spesialisthelsetjenesten og primærhelsetjenesten, apotekene inkludert. Helsedirektoratet bør ha en sentral rolle som koordinator og fasilitator i nettverksarbeidet.

Helsedirektoratet har sett det som viktig å samle kunnskap og å spre denne kunnskapen ikke bare i helsesektoren, men også til andre samfunnssektorer. Det har således vært avholdt flere konferanser om inneklima, lokal luftkvalitet, pollen og planter, matallergi, helseplager tilskrevet miljøfaktorer samt de årlige konferansene kalt Allergifrisk (strategikonferanser). I tillegg er det utarbeidet informasjonshefter. I 2014 og 2015 vektlegges arbeidet med de landsomfattende konferansene («Krafttak for et bedre skolemiljø») for å få alle skoler godkjent etter forskriften om miljørettet helsevern i barnehager og skoler.

Helt grunnleggende er også behovet for å sikre en lang rekke «grunnlagsdata» som vil gjøre det mulig å se om de ulike tiltakene virker og hva man har oppnådd. Det er akutt behov for bedre oversikt over nær sagt alle parametre knyttet til AAO – langs hele aksen fra forebygging til behandling, oppfølging og mestring.

Hovedgrep i det nye programmet

Med bakgrunn i erfaringen fra andre nordiske land er det særlig fire områder som peker seg ut: Styrket nettverksarbeid, styrket forskning og det å fullføre etableringen av regionale astma-, allergi- og overfølsomhetssentre (AAO-sentre). Bedre og mer forskningsbasert informasjon til befolkningen skal gjøres tilgjengelig gjennom www.helsenorge.no, og gjennom kunnskapsspredning og kompetansebygging i helsetjenesten og andre sektorer.

1. ASTMA OG ALLERGI SOM NASJONAL UTFORDRING

I dette kapitlet gis en oversikt over definisjoner og avgrensninger, status etter gjeldende handlingsprogram, forekomst og samfunnskostnader ved astma, allergi og overfølsomhet samt erfaringer fra våre naboland.

1.1 Definisjoner og avgrensninger

Astma er en kronisk betennelse i nedre luftveier som fører til hevelse av slimhinnene, sammentrekning av muskulatur i luftveiene og slimopphopning. Resultatet blir trange luftveier og anfall med hoste, tung pust og piping i brystet.

Årsakene til astma er bare delvis kartlagt, og mange faktorer er sannsynligvis av betydning. Astma kan være arvelig, men nyere studier viser at flertallet av barn med astma ikke har allergiske foreldre. Allikevel har barn der foreldrene har astma, allergi eller atopisk eksem, større risiko for å utvikle astma. Personer med allergi har oftere astma enn andre, men allergi kan også manifestere seg etter de første astmasymptomene. Eksponering for tobakk gjennom svangerskap og tidlig i livet øker risikoen for astmautvikling. Astma kan være utløst av IgE- antistoffer som har gitt en allergisk lidelse eller den kan skyldes annen overfølsomhet (se nedenfor).

Astmasymptomer utløses oftest i barnealder av virus, særlig hos barn med allergier. Men også pollen, pelsdyr, irritanter, og spesielt sigarettrøyk, bidrar hyppig til å forverre astma i tillegg til husstøvmidd, fugler, parfyme, luftforurensning ute og inne (inneklimaproblematikk), muggsopp, støv fra mel og andre allergener. Andre ytre påkjenninger som varme eller kulde, fysisk aktivitet, væromslag, emosjonelle reaksjoner kan også utløse et astmaanfall. Inntak av enkelte legemidler som acetylsalisylsyre (Aspirin, Globoid), andre ikke-steroide antiinflammatoriske midler (NSAIDs), og betablokkere (særlig ikke-selektive) kan forverre astma. Ny kunnskap viser at barneastma øker risikoen for KOLS.

Overfølsomhet kan vise seg i form av symptomer som kan reproduseres og som utløses av definerte stimuli som tåles av den øvrige befolkningen.

Allergi er en overfølsomhetsreaksjon som skyldes immunologiske mekanismer, enten via antistoff eller celler. De fleste allergiske reaksjoner skyldes IgE-antistoffer ved kontakt med substanser i mat eller i omgivelsene for øvrig (i de aller fleste tilfellene knyttet til proteiner). En stor gruppe allergier gir også hudplager, særlig kontakteksem.

Til de allergiske sykdommene/symptomene hører:

- Astma
- Allergisk rhinitt
- Atopisk dermatitt (kontakteksem)
- Urticaria (elveblest)
- Angioødem (ødematøs hevelse i underhuden/slimhinnene i luftveiene som kan gi opphav til kvelningssymptomer)
- Allergisk sjokk
- Fødemiddelallergi (kvalme, oppkast, magesmerter, diaré)
- (Flere av disse sykdommene kan opptre sammen = co-morbiditet)

De vanligste proteinene og kjemikaliene som kan utløse en allergisk reaksjon, dreier seg om

- Pollen
- Dyrehår (flass, sekreter)
- Kumelk-protein
- Egg
- Fisk
- Peanøtter
- Nøtter og frø
- Husstøvmidd
- Muggsopp
- Kjemiske stoffer ved hudkontakt (f. eks nikkel, duftstoffer, konserveringsmidler)
- Småmolekylære kjemiske stoffer som kan gi allergi og annen spesifikk overfølsomhet i luftveiene (f. eks isocyanater, organiske syreanhybrider, kvartære ammoniumforbindelser)
- Medikamenter
- Insekter (veps og bier)

I tillegg er flere miljøgifter vist å ha en rolle i astma og allergi, men mekanismene er ikke kjent. Miljøgifter er biologisk aktive molekyler som er fremmede for en organisme, d.v.s. kroppsfremmede stoffer som organismen ikke lager selv, men som lages i omgivelsene. Flere av disse stoffene blokkerer bestemte fysiologiske prosesser og er derved giftige, f. eks. ftalater, triklosan og fenolen.

Atopi er en arvelig predisponering for allergiske reaksjoner, dvs. tendensen (personlig eller familiær) til å produsere IgE-antistoffer som svar på allergen (som regel proteiner) uten at det nødvendigvis gir typiske sykdomsbilder som atopisk eksem, «høysnue» eller allergisk astma.

Atopisk eksem er en kronisk, inflammatorisk og kløende hudsykdom, med dårligere fungerende hudbarriere mot bakterier, virus og allergener. Eksem disponerer for utvikling av allergensensibilisering som igjen disponerer for andre allergiske sykdommer. Det er vist at atopisk dermatitt i første leveår gir sterkt økt risiko for astma og/eller pollenallergi når man når skolealder.

Undersøkelser har vist at familiers livskvalitet kan bli alvorlig påvirket av å ha et barn med atopisk eksem. Flere studier har vist at søvnforstyrrelser, nedsatt konsentrasjon, psykososiale problemer, mye tid til behandling, reduserte muligheter for fritidsaktiviteter eller redusert yrkesvalg fører til nedsatt livskvalitet hos affisert pasient, men også hos foreldre og søsken.

Atopisk eksem er en kronisk sykdom som innebærer økte samfunnskostnader i form av fravær fra skole og jobb (for pårørende og for den voksne pasienten), utgifter knyttet til behandling som kan være både krevende, behandling flere ganger i døgnet, og komplisert fordi ulik grad av eksem krever ulik behandling, hyppige legebesøk samt innleggelser. Undersøkelser viser også stor bruk av udokumentert behandling som i stor grad må dekkes av familiene selv.

Allergi og atopi begrepene brukes ofte noe om hverandre. Det viktigste er å skille mellom allergisk sensibilisering, altså påvist allergiantistoff i blod eller reaksjon ved allergitesting i hud på den ene siden og klinisk allergi på den annen hvilket innbefatter en reaksjon på allergenet med en allergisk sykdomsmanifestasjon.

Ikke-allergisk overfølsomhet brukes som betegnelse på overfølsomhetsreaksjoner der immunologiske mekanismer ikke kan påvises. Tidligere brukte man ordet «intoleranse» som et samlebegrep om all overfølsomhet som ikke skyldtes allergi. I fagmiljøet brukes det nå stort sett bare for tilstander med sukkermalabsorpsjon som i laktose- og fruktoseintoleranse.

Stoffer (påvirkningsfaktorer) som kan (eller som av noen oppleves kan) forårsake ikke-allergisk overfølsomhet inkluderer blant annet:

- Toksiske stoffer
- Mat og drikke som inneholder høy konsentrasjon av histamin eller andre biogene aminer
- Organiske syrer (fra frukt, bær eller grønnsaker)
- Tilsetningsstoffer i mat (E220 – E228)
- Andre konserveringsmidler
- Andre matvarer (som kan gi eosinofil mage-tarm sykdom)
- Laktose
- Stoffer som avgir dufter

De tilstandene som sees i forbindelse med ikke-allergisk overfølsomhet, kan være:

- Irritabel tarm
- Uspesifikk småbarns diaré
- Protein-indusert enterocolitt-syndrom
- Obstipasjon
- Spedbarns kolikk
- Migrene
- Astma (se ovenfor)

1.2 Status etter forrige strategi

Den foregående strategien har ikke lykkes med å nå det overordnede målet om å redusere forekomsten av astma og allergi. Når det gjelder forebygging har vi imidlertid oppnådd resultater. Det er gjennomført betydelige tiltak for å fjerne årsakene til veksten, og for å fjerne faktorer som gjør det krevende å leve med sykdommene. Det er økt samhandling mellom alle samfunnssektorer og mellom myndigheter,

fagmiljøer og frivillig sektor. Et eksempel er veimyndighetenes tiltak for å redusere lokal luftforurensning fra utslipp fra kjøretøy. Samarbeid om inneklima skjer mellom alt fra byggetekniske fagmiljøer til lokale skoleeiere.

Andelen barn som utsettes for passiv røyking, har gått betydelig ned de siste årene, men det er fortsatt et stykke igjen til at alle barn vokser opp i røykfrie omgivelser. Studier viser at eksponering for passiv røyking i fosterlivet kan gi utvikling av astma, og det er funnet økt hyppighet av astma blant barn som vokser opp blant røykende foreldre. Mors røyking er dokumentert å gi redusert lungefunksjon hos det nyfødte barnet.

I tillegg viser den samlede kunnskapen knyttet til helseeffekter av fuktskader og muggsopp i inneklimaet, at slik eksponering ikke bare er knyttet til forverring av astma, men også til utvikling av sykdommen. Andre påvirkningsfaktorer for utvikling av allergi er forurensninger i uteluft. Spesielt gjelder dette forbrenningspartikler (dieseleksospartikler og vegslitasjestøv). Forverrende miljøfaktorer er dårlig inneklima, arbeidsrelaterte forurensninger både i industrielt og ikke-industrielt arbeidsmiljø, svevestøv, kjemikalier, sterke lukter og allergener pollen, dyrehår, mat m.m.

Astma, allergi og overfølsomhet er en individuell sykdom med mange faktorer og variasjoner rent biologisk. Det betyr at de færreste kan behandles likt. Det er viktig at legene har oversikt over dagens kunnskapshuller og vet hva som er usikkert. En astma og/eller allergidiagnose skal ikke stilles bare på grunn av prøver, men på en helhetlig vurdering. Allergi som diagnose skal stilles på legekontoret, ikke i laboratoriet. Testene er kun en støtte som gir indikasjoner på allergier.

1.3 Forekomst

Miljø- og barneastma-undersøkelsen i Oslo fulgte 1019 barn født i Oslo 1991-92 frem til 10 års alder og 550 til 16 års alder. Blant 10-åringene hadde 11 prosent aktiv astma mens 20 prosent hadde hatt astma så langt i livet. Blant 16-åringene hadde 13 prosent aktiv astma mens 27 prosent hadde hatt eller hadde astma fortsatt. Den samme undersøkelsen viser at enda flere barn er sensibilisert for allergi. Resultatene ved 10 års alder viser positiv prikktest hos 27 %. Ve 16-års alder er dette økt til 45 %. Dette sammenfaller med WHO's prognose for allergisk sykdom som antyder at 50 % av befolkningen vil ha en eller annen allergisk manifestasjon i 2030, gitt at utviklingen fortsetter som nå.

Nyere tall viser at 16 % av to-åringene i Trondheim hadde atopisk eksem (Smidesang 2010). 70% av tilfellene hadde et mildt eksem. Hos ungdom med atopisk eksem varierte selvrapporterte mentale plager både med alder og kjønn. De eldste ungdommene rapporterte mer plager. I motsetning til toåringene, der flere gutter enn jenter hadde allergirelaterte sykdommer, rapporterte flere jenter enn gutter slike plager i tenårene. I tillegg er det undersøkelser fra Sør-Varanger hos skolebarn som viste at 23,6 % har eksem. Hos ca. 30 % av barn med moderat til alvorlig eksem regner man med at matallergener spiller en rolle for sykdommen. (Dotterud et al 2007)

Astma og allergi er, i motsetning til andre kroniske sykdommer som f. eks. diabetes og kreft, kjennetegnet ved at de starter tidlig i livet og i stor grad forblir der livet ut. (The European Lung White book2014)

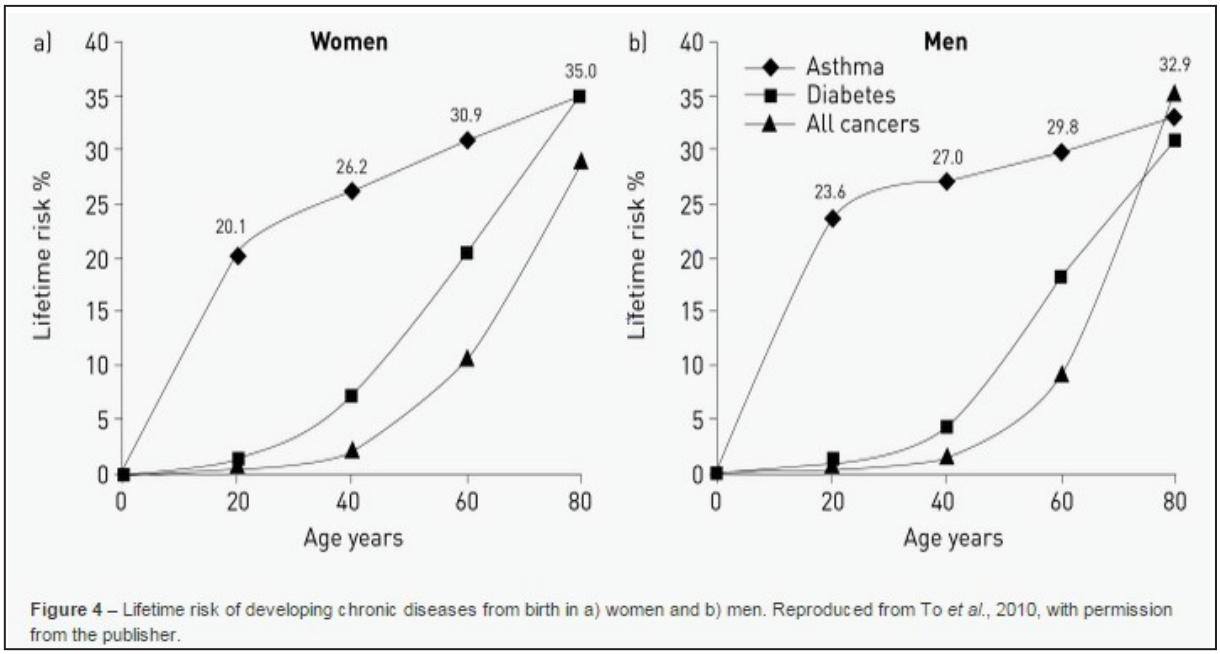
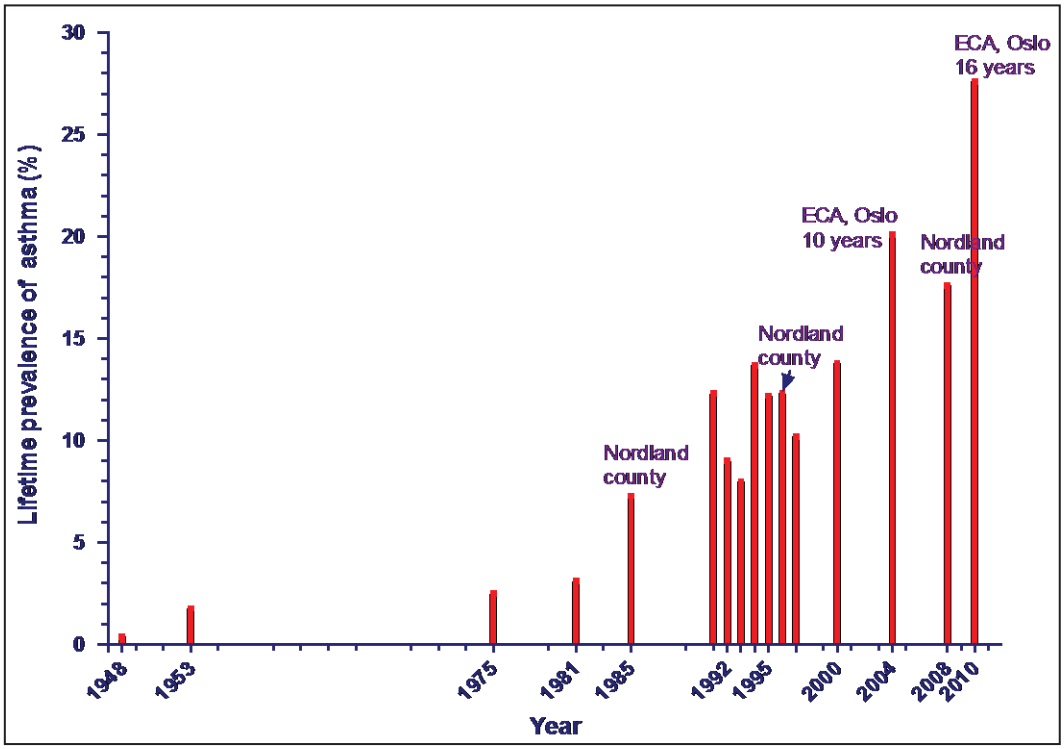


Figure 4 – Lifetime risk of developing chronic diseases from birth in a) women and b) men. Reproduced from To *et al.*, 2010, with permission from the publisher.

Kurven nedenfor viser forekomsten av astma i Norge (1948 -2010) basert på studier hos barn (ECA= Miljø- og barneastmastudien i Oslo).



I 2005 viste tall fra Hordaland og Oslo at 8-10 prosent av voksne hadde astma.
The European Lung White book for 2014 viser at forekomsten av astma i alderen 18-44 år nå er høyere enn 10% i Nord- og Vest-Europa.
Allergiske sykdommer har økt i alle vestlige land de siste 30-40 årene. Når for eksempel pollenallergi øker – kan også allergiske reaksjoner på mat øke, siden pollenallergi kan gi kryssreaksjoner mot visse frukter, grønnsaker og nøtter. Selv om forekomsten av pollenallergi er vanskelig å fastslå helt nøyaktig, må vi fastslå at forekomsten er relativ høy i Norge og at pollenallergi er den hyppigst forekommende allergien. Det er anslått at over 20 % av befolkningen reagerer mot en eller flere typer pollen. (*Bolle R 2014*). Flere debuterer i voksen alder. Nyere forskning tyder også på at eksponering for fuktskader og muggsopp i inneklimaet ikke bare er knyttet til forverring av astma, men også til utviklingen av sykdommen.

Arbeidsrelatert astma omfatter både yrkesastma (arbeidsbetinget=jobben er årsak, i betydningen sykdommen ville ikke oppstått om det ikke var for eksponeringer i arbeid) og arbeidsforverret astma. Både yrkesastma og arbeidsforverret astma kan være hhv allergiske og ikke-allergiske årsaker. Det er anslått at 28 prosent av alle voksne legediagnostiserte astmatikere i Hordaland har arbeidsrelatert astma (*Bakke PS, Gulsvik A. Int J Lung Dis 2000.*). Hos personer i Midt-Norge i alderen 18-55 år som hadde vært sykmeldt for astma >16 dager i årene 2000-03, anga 70 % at de hadde arbeidsforverret astma (Leira et al 2006). Det var flere tilfeller med yrkesforverret astma fra ikke-industrielle yrker enn fra industrielle yrker.

1.4 Samfunnskostnader

At så mange har plager, har store konsekvenser for de som rammes og deres pårørende, samtidig som det gir store utfordringer til helsevesenet.

Det er beregnet at astma, allergi og andre overfølsomhetsreaksjoner koster det norske samfunnet mellom 7 og 10 milliarder kroner pr. år. Dette er et estimat basert på beregninger foretatt i andre land, først og fremst Sverige og Finland. Når det gjelder arbeidsrelatert astma, er det beregnet at det samfunnsøkonomiske tapet beløper seg til 1,9 milliarder kroner i året 2005, målt i 2007-priser (Arbeidstilsynet 2008 etter Leira et al 2006). Dette skyldes sykefravær, uførhet, medisiner på blå resept og legehandling, samt skattefinansieringskostnader.

I Finland er det for året 2011 beregnet at *direkte* kostnader i forbindelse med astma og allergi, beløp seg til 319 millioner Euro. I dette beløpet ligger det utgifter til medikamenter, sykehusopphold, polikliniske undersøkelser, rehabilitering og spesialdietter i skolene. Av dette beløpet stod astma alene for 65 % av *alle* kostnadene og halvparten av utgiftene til medikamenter. Hvis man til beløpet på 319 millioner Euro legger til de *indirekte* kostnadene knyttet til sykefravær, uførepensjon og produksjonstap, beløper de totale utgiftene i det finske samfunnet seg til mellom 1,3 og 1,6 milliarder euro i 2011 når det gjelder astma og allergi. Finland har 5,4 millioner innbyggere.

I Sverige har man sett nærmere på hva astma alene koster. Basert på en undersøkelse publisert i 2007 kostet hvert astmatilfelle hos personer i alderen 25 – 56 år i gjennomsnitt 15919 svenske kroner; av dette utgjorde 31 % direkte kostnader og 69 % indirekte kostnader. Basert på antallet astmatikere i den aktuelle aldersgruppen, ble det beregnet at astma alene kostet Sverige 3,7 milliarder svenske kroner pr. år. Et anslag foretatt i den artikkelen hvor undersøkelsen er publisert, viser at dersom man inkluderer de under

25 år og de over 56 år i beregningene, ville utgiftene til astma ha blitt doblet, d.v.s. til ca. 7,4 milliarder svenske kroner. Omregnet til Norge skulle det ut fra folketallet tilsi at vi her i landet har utgifter på ca. NKR 3.3 milliarder til astma årlig. I tillegg kommer utgiftene til alle andre former for allergier og andre overfølsomhetsreaksjoner.

I et estimat bare for pollenallergi er det anslått en årlig kostnad pr. pasient på kr. 10.000 (European Allergy White paper 1993). Med et anslag på opp mot 1 million norske allergikere, blir den årlige summen på rundt 10 milliarder kroner (kfr. ovenfor). I Danmark er kostnadene til hver pollenallergiker i 2009 beregnet til kr. 7.500. En nyere studie viser at hvis gresspollen- og/eller husstøvmidd-allergikere behandles med vaksinasjon, så kan det årlige antall dager med symptomer reduseres fra gjennomsnittlig 189 dager pr. år før behandling til 145 dager etter behandling. Tilsvarende vil antall sykedager bli redusert fra 3,7 til 1,2 dager årlig. De behandlede allergikernes livskvalitets-score svarte til en årlig økning i størrelsesorden 0,03 0,06 QALY (Quality Adjusted Life Years) pr. pasient.

En utredning av samfunnsøkonomiske kostnader ved dårlig inneklima i Norge er foretatt i 2014 (Bakke JV). Det en nær sammenheng mellom dårlig inneklima og sykelighet av luftveislidelser, luftveisinfeksjoner, astma, allergi og andre overfølsomhetsreaksjoner. Fuktskader i boliger anslås å stå for 20 % av denne sykeligheten i Norge.

Estimert årlig innsparing ved redusert forekomst av allergiske sykdommer er beregnet slik:

2% redusert forekomst	**140 mill NOK**
5%:	**350 mill NOK**
10%:	**700 mill NOK**
20%:	**1.4 mrd NOK**

1.5 Erfaringer fra våre naboland

Finland er inne i sitt nye allergiprogram som gjelder for 2008-2018. De finske resultatene er så langt lovende både når det gjelder reduksjon av samfunnskostnader og i å snu økningen av astma og allergi (se vedlegg). Finland konkluderer med at allergiparadigmet trenger reevaluering når allergiske personer er i ferd med å utgjøre flertallet i den vestlige befolkningen, og kostnadene er økende. De viser til at de hadde en betydelig kostnadsreduksjon i astmaprogrammet (2007 ca. 250 millioner euro og 227 millioner euro i 2011).

I Danmark har de bygd opp Allergisentre, som vurderes som en arbeidsform som både er effektiv og ressurssparende for pasienter og personell. Erfaringene fra Allergisenteret i Odense styrket oppfattelsen av at den komplekse pasient trenger tverrfaglig utredning og behandling, spesielt gjelder dette matallergier/matoverfølsomhet. Erfaringer fra Arbeidsmedisinsk avdeling i Odense viser at senteret yter verdifull bistand til det lokale folkehelsearbeidet i regionen.

2. NASJONALE MÅL FOR 2015 TIL 2024

Dette kapitlet inneholder mål og delmål for programperioden. Kapitlet redegjør for utfordringen i og kompleksiteten ved å redusere forekomst og samtidig lette byrden ved å leve med astma, allergi og overfølsomhet.

2.1 Grunnlagsdata og forskning

Både innenfor miljørettede tiltak, behandling, forekomst, utvikling og de fleste andre områder er datagrunnlaget for dårlig til at det er mulig å monitorere utviklingen fra år til år. Det er et problem i seg selv at vi ikke kan si at vi har tilstrekkelig oversikt over problemomfanget og effekt av tiltak, og det er et betydelig hinder for mer og bedre forskning. Det vil være avgjørende for å måle effekten av programmet at vi har gode grunnlagsdata. Programmets første år vil ha som et primærmål å skaffe slike tilgjengelige data, enten fra registre eller gjennom studier. Når datagrunnlaget er på plass, kan vi definere mer presise og målbare mål og utarbeide presise og målbare tiltak

2.2 Overordnede mål

Finland har vist at ved relativt enkle virkemidler, har de ved 5 års evaluering vist en betydelig endring til det bedre. Det finske samfunnet har et klart mål å redusere byrden.

Overordnet mål:

Færre utvikler AAO

Indikator: Forekomsten av personer med astma, allergisk rhinitt, atopisk eksem og kontakteksem reduseres med 20 prosent.

Mål for diagnostikk og behandling:

Bedre utredning og mer presis diagnostikk

Indikator: Alle fastleger skal i løpet av perioden 2015 – 2019 gjennomgå faglig oppdatering og verktøy for riktig diagnostisering, livsstils- og kostveiledning.

Behandling av alvorlige allergier (anafylaksi) er optimalisert

Andelen akuttinnleggelser er redusert med 40 prosent

Færre opplever episoder med forverring

Indikator: Andelen diagnostiserte som legges inn med forverring er redusert

Indikator: Allergikontrollkort og astmakontrollkort for egen-mestring benyttes i hele landet

Delmål forebygging:

Ingen barn eksponeres for passiv røyking

Indikator: Her følges de nasjonale målsettinger, og det tilstrebes å følge FN's barnekonvensjon som sier at barn har rett til oppvekst i et miljø som ikke er helseskadelig.

Kunnskapsmål befolkning:

Befolkningen har økt kunnskap om hva de kan gjøre for å redusere risikoen for å utvikle astma og allergier

Toleransen for allergener i befolkningen er økt

Indikator: Antall personer med matallergidietter (i skoler, barnehager og eldreinstitusjoner) reduseres med 50 prosent.

Arbeidsrelaterte allergier og andre arbeidsrelaterte overfølsomhetsreaksjoner er redusert

Indikator: Antallet personer med yrkesbetingede allergier/overfølsomhetsreaksjoner i arbeidslivet reduseres med 50 prosent.

Flere opplever mildere forløp

3. PROGRAMMETS HOVEDSØYLER

Programmet er organisert innenfor de tre hovedsøylene *nettverk, forskning og informasjon/kompetanse*. Vi beskriver også oppbyggingen av de regionale astma, allergi og overfølsomhetssentrene.

3.1 Regionale astma-, allergi og overfølsomhetssentre

I november 2010 bestemte Helse- og omsorgsdepartementet at det skal opprettes tverrfaglige kompetansemiljøer på astma og allergi. Kompetansemiljøene er senere blitt konkretisert og omtales nå som regionale sentre for astma, allergi og andre overfølsomhetsreaksjoner. Sentrene skal stå for rådgivning og opplæring til den lokale helsetjenesten for å sikre et best mulig behandlingstilbud lokalt for den enkelte pasient. Målet med disse sentrene er å sørge for et tettere samarbeid mellom fagfolkene for å sikre at pasienter får rett diagnose og avdekke eventuell feilbehandling. Kompetansemiljøene skal bedre kunnskapen om astma og allergi både i sykehus og ute i kommunene. De regionale AAO-sentrene skal også ta opp forskningsoppgaver og således knytte forskere til seg. Særlig når det gjelder reaksjoner på mat, er det et stort behov for mer presis diagnostikk og avklaring av hvilken type tiltak som bør iverksettes.

AAO-sentrene skal virke både som kompetansetjeneste og behandlingssenter for henviste barn, unge og voksne med komplekse sykdomsbilder. Allergisentrene bør sikres nødvendig kompetanse og kapasitet slik at de også kan gi faglig støtte til kommunenes miljørettede helsevern, kommunene for øvrig og andre som trenger slik bistand. Dette er på samme måte som de arbeidsmedisinske avdelingene har ytet støtte til bedriftshelsetjenestene rundt om i landet.

De fire RHFene har besluttet å opprette disse sentrene som vil være helt sentrale i fremtidig diagnostikk, behandling, forskning samt kompetanse og nettverksbygging. En viktig begrunnelse for å ha etablerte *sentre,* er behovet for å kunne utføre provokasjonstester på en forsvarlig måte.

Skissen nedenfor har vært brukt for å illustrere AAO-sentrenes plass i forhold til de andre kliniske avdelingene i de fire universitetsklinikkene, men også andre kliniske sykehusavdelinger i landets helseforetak. Det er også tatt hensyn til forholdet til primærhelsetjenesten.

Under arbeidet med kompetansemiljøene har det blitt tydelig at de regionale avdelingene for arbeidsmedisin ved universitetssykehusene i Oslo, Bergen, Trondheim og Tromsø har mye erfaring fra ofte komplisert utredning og oppfølging av personer utsatt for faktorer i arbeidsmiljøet. Dette er bakgrunnen for at AAO-programmet foreslår at AAO-kompetansesentrene blir vurdert lagt til nettopp de fire regionale helseforetakenes avdelinger for arbeidsmedisin. Bl. a. vil man her, under kontrollerte betingelser, kunne utføre provokasjonsforsøk som ledd i pasientutredninger.

De utredninger som er gjort, fremholder at hvert senter bør ha et begrenset antall ansatte og at hovedtyngden i arbeidet skjer mellom senteret og de kliniske avdelingene på sykehuset, men også mellom senteret og andre sykehus og helsetjenesten og miljørettet helsevern ute i kommunene. Typiske samarbeidsavdelinger for det regionale AAO-senter vil således være avdelinger for lungesykdommer, øre-nese-hals, barnesykdommer, gastrointestinale lidelser, psykiatri, hudsykdommer, arbeidsmedisin, anestesi og farmakologi samt allmennmedisin og miljørettet helsevern.

3.2 Nettverksarbeid

Gode og robuste faglige nettverk kan og bør supplere de regionale kompetansesentrene for å sikre nasjonal og lokal kompetansflyt og informasjonsspredning. Helsedirektoratet har etablert et nettverk mellom de eksisterende regionale astma-, allergi- og overfølsomhetssentrene for å sikre erfaringsoverføring og fordeling av oppgaver mellom dem. I tillegg skal det etableres nettverk mellom de enkelte sentrene, de privatpraktiserende spesialister og aktører i primærhelsetjenesten. Nettverkene etableres både nasjonalt, regionalt og interkommunalt.

Helsedirektoratet tar sikte på å være ansvarlig for etablering og drift av nettverket og sikre en hensiktsmessig informasjonsstrøm, basert på moderne informasjonsteknologi, men også tilrettelegging for kurs og veiledningsvirksomhet. Implementering av tiltak vil være naturlig å gjennomføre gjennom nettverket. Nettverksarbeidet vil omfatte kompetanseoppbygging og vedlikehold innad i helsevesenet både i primær- og spesialisthelsetjenesten. Frivillige organisasjoner bør delta i nettverket på nasjonalt, regionalt og lokalt nivå.

Helsetjenesten i kommunene bør delta i et regionalt AAO-nettverk, fortrinnsvis med deltakelse fra kommuneoverlege og miljørettet helsevern, minst en helsestasjon og en fastlege i hver kommune.

Apotekpersonell har en veilederrolle i forhold til inhalasjonsmedikamenter og bør inkluderes i lokale nettverk. Legen kan i større grad etterspørre veiledning i apoteket til pasientgrupper med særlig informasjonsbehov og hvor bedret etterlevelse gir en særskilt helsegevinst, som f. eks. kontroll av inhalasjonsteknikk med astma. Det kan utvikles mulighet i e-resept slik at lege kan ordinere informasjon fra apotek.

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3.3 Informasjon og kompetansebygging

God informasjon til befolkningen vil bidra til at flere kan redusere risikoen for å utvikle AAO, og bidra til å gjøre det lettere å leve med plager. Å bygge bredere forståelse for tiltak de med AAO vil ha nytte av vil gi større gjennomslagskraft også for tiltak og virkemidler som kan oppleves som en inngripen i den enkeltes frihet.

Helseforetakenes Lærings- og mestringssentre (LMS) skal kunne gi tilbud til pasienter (og pårørende) som har AAO. Tilbudet kan enten foregå ved at pasienter deltar på kurs ved LMS-ene
– eller ved at LMS-ene tilbyr kurs til helsepersonell i kommunene.

Etter mønster fra Finland bør kommunene vurdere å inngå avtaler med ett eller flere legesentre for å tilby god lokal opplæring av pasienter og pårørende. På samme måte bør en eller flere helsestasjoner styrke sin kompetanse innen fagområdet. Kommunene bør prioritere ressurser i klinisk ernærings-fysiologi og fysioterapi for veiledning og opplæring av personer med en AAO- diagnose.

Det er etablert astmaskoler, eksemskoler, matskoler og inneklimaskoler som pasientrettede tiltak. Det er viktig at slike tilbud blir mest mulig ensartede, uansett hvor i landet de blir etablert. I løpet av 10-årsprogrammet bør det startes forskning på interaktiv kommunikasjon/e-læring brukt i undervisning og konsultasjoner.

Norges astma- og allergiforbund bør sikres ressurser til nødvendig råd- og veiledningsvirksomhet overfor befolkningen.

Befolkningen skal ha tilgang til god, relevant og tilstrekkelig informasjon. Informasjon skal være tilgjengelig på Helsenorge.no og i kontakt med helsetjenesten.

Pollenvarslingen har nå eksistert siden 1976. Mange oppgir at tjenesten er nyttig, men at den har et utviklingspotensial. For å vite mer om hva slags nytte tiltaket har for de med AAO, bør varslingen evalueres.

Helsedirektoratet skal gjennom dialog med utdanningsmyndighetene sikre grunnleggende opplæring av lærere i skolen slik at skolen i større grad kan tilrettelegge for deltagelse i gym og lek. Det gjelder også tilrettelegging for matallergidietter og optimal bistand ved akutte symptomer ved allergiske sykdommer. Skolehelsetjenesten bør sikres kompetanse så de kan bidra til korrekt tilrettelegging for elever.

Det etablerte kompetanseområdet i allergologi ble opprettet av Legeforeningens landsstyre i 2012. Det ble samtidig vedtatt en overgangsordning for godkjenning av spesialister med langvarig praksis. Innholdet i utdanningen bør videreutvikles.

I tillegg bør helsepersonell i primærhelsetjenesten få nødvendig kompetanse i å veilede i primærforebyggende tiltak og erfaring fra diagnostikk og behandling, opplæring og oppfølging.

For å sikre riktig legemiddelbehandling er det viktig at helsepersonell samarbeider. Å bygge strukturer som legger til rette for tverrfaglig samarbeid rundt pasientens legemiddelbruk er nødvendig. Aktuelle arenaer for tverrfaglig samarbeid er legemiddelkomiteer, lærings- og mestringssenter, kommunefarmasøyt, legemiddelpoliklinikk og klinisk farmasi.

3.4 Forskning og utvikling

Finland har valgt å snu opp ned på en del gamle myter og råd for forebygging. De finske rådene gis nå med utgangspunkt i biodiversitetshypotesen og forskning. Norske anbefalinger bygger i liten grad på solid forskning – mye fordi vi fortsatt vet for lite om årsakssammenhengene. Det er et akutt behov for et omfattende forskningsprogram som omfatter årsaker, utløsende faktorer, faktorer som beskytter, og innenfor behandling, oppfølging og mestring.

Det er satt i gang større internasjonale initiativ som Norge deltar i. Ett eksempel er Prevent ADALL (Preventing Atopic Dermatitis and ALLergies in children) som har fått forskningsstøtte fra Helse Sør-Øst som en starthjelp for de første 3 år. PreventADALL vil gjennom internasjonalt samarbeid og nasjonal forankring etablere en intervensjons fødselskohortstudie med informasjon fra tidlig svangerskap og frem til iallfall tiårs alder for å teste en primærforebyggingsstrategi med langtidseffekt på allergiske sykdommer. Innsamling av biologisk materiale og tett oppfølging av barnet i tidlig spedbarnsalder er sentrale elementer i studien.

Det er behov for forskning som vil gripe inn i de fleste samfunnssektorer. Forskningen bør ta sikte på å avdekke de komplekse årsakssammenhengene hvor arv, miljø og livsstil spiller tett sammen i utvikling og videre sykdomsforløp.

Det er behov for basalforskning på mekanismer, klinisk forskning på utprøving av behandling, helsetjenesteforskning på hvordan helsetjenesten best organiserer diagnostikk, behandling og forebygging, og intervensjonsstudier hvor man prøver ut tiltak.

Fra flere studier er det indikasjoner på at bruk av Probiotika («gode» bakterier i tarm og øvre deler av kroppen) kan ha gunstig effekt på utvikling av allergi, men funnene er ikke entydige.

Det antas, men er ikke foreløpig vist, at reduksjon i forekomst av en allergisk sykdom som opptrer tidlig, som atopisk eksem eller fødemiddelallergi, kan forebygge utvikling av relatert allergisk komorbidiet, d.v.s. samtidig tilstedeværelse av én eller flere lidelser eller tilstander utover hoveddiagnosen.

Det å vokse opp på gård eller i miljøer med stort biologisk mangfold, har vist å ha en sammenheng med redusert forekomst av astma, allergisk rhinitt og allergisk sensibilisering. Selv om det ikke er gjort intervensjonsstudier av oppvekstmiljø, har intervensjonsstudier med Probiotika basert seg på en tilsvarende tilnærming: at «gode» bakterier i tarm og øvrige deler av kroppen er avgjørende for normal utvikling av immunsystemet med derav redusert forekomst av atopisk eksem.

Developmental origins of Health and Disease (DoHaD) er et strategisk forskningsfokus innen mange ulike sykdomsgrupper som har til felles at hendelser forut for, rundt og etter konsepsjon og gjennom svangerskapet kan ha stor betydning for senere sykdom. Forskning innen det humane mikrobiom har, parallelt med DoHaD-tilnærmingen, et stort internasjonalt forskningsfokus, med økende forståelse for det helt nødvendige samspillet mellom mikrobiologisk mangfold innad og inn mot den menneskelige organisme og immunsystemets utvikling for å forebygge sykdom. Et mikrobiom er det økologiske samspillet mellom alle bakterier, «normale» og potensielt sykdomsfremkallende, i en persons kropp.

Det mangler også kunnskap om hvilken rolle barrierer i hud og luftveier spiller for utvikling av allergiske sykdommer og når en i utgangspunktet normal barriere blir redusert og hvilke implikasjoner dette får for immunologisk utvikling. Her er miljøer i Norge i ferd med å bygge opp, som ledd i et internasjonalt samarbeid, forskning ved starten av livet og med planer om langtidsoppfølging av en ny fødselskohort som rekrutteres ved 18 ukers gestasjonsalder i en studie som startet opp primo 2015 (Prevent ADALL – Preventing Atopic Dermatitis an ALLergies). Prevent ADALL er en multisenter fødselskohortstudie som etableres i Norge sammen med ett senter i Sverige, med internasjonalt samarbeid. Studien har som formål å undersøke om allergisk sykdom kan forebygges hos barn gjennom intervensjoner i første leveår. I tråd med nyere Europeisk forskning ser man blant annet på tiden for introduksjon av matvarer ved siden av amming. Internasjonale retningslinjer har i mange år fulgt tanken om at utsatt introduksjon kunne forebygge allergi. Dette er nå godt dokumentert å ikke være korrekt. I en omfattende oversiktsartikkel har den Europeiske allergiforeningen gjort rede for all tilgjengelig forskning frem til 2014, som konkluderer med at det ikke er holdepunkter for at fravær av fødemidler frem til 6-måneders alder forebygger utvikling av allergi eller intoleranse. Snarere er det en bekymring for at manglende tidlig introduksjon kan ha bidratt til økt allergiutvikling. (Food Allergy and Anaphylaxis Guidelines 2014, EAACI)

Noen få, veldokumenterte risikofaktorer kan forebygges, selv om det ikke er så mange intervensjonsstudier som tester effekten av disse. Eksponering for tobakksrøyk og fuktskade i hus er slike områder. For tobakksrøyk er det i dag ikke behov for ny forskning for å påvise skadelige effekter på astma da dette er godt kjent. FHI leverte i 2014 en rapport hvor de oppsummerer forskning om sammenhengen mellom snus og elektroniske sigaretter i svangerskap og småbarnsfasen, og effekter på forekomst/utvikling av AAO hos barn.

Noen miljøfaktorer fases ut gjennom nytt regelverk og nye faktorer kommer til. Det er behov for en mer offensiv og systematisk tilnærming til disse faktorene. Eksempler er emisjoner fra nye byggematerialer,

overflatebehandling, rehabilitering, rengjøring og vedlikehold. For fuktskader i hus er det heller ikke klart hvilke mekanismer som er involvert i sykdomsutvikling, og det er derfor behov for mer forskning for å identifisere optimale forebyggende strategier.

Det er solid dokumentasjon på at det å bo nær trafikkerte veier gir forringet lungefunksjonsutvikling og økt risiko for astma. Samtidig mangler gode intervensjonsstudier som vurderer effekten av å redusere nivået av trafikk-relaterte partikler. Det mangler kunnskap om hvilke egenskaper ved partiklene som gir helseeffekter, og om det finnes en sammenheng mellom luftforurensning og pollen i utviklingen av astma og allergisk rhinitt. Det er indikasjoner for at luftforurensning kan påvirke mengden og aktiviteten av pollenallergener. Svevestøv, nitrogendioksid og ozon kan gi større frigjøring av allergener fra pollenkornene, noe som gjør at allergenene er mer tilgjengelige for inhalasjon. Studier har også vist at nitrogendioxid og ozon kan øke allergenets aktivitet ved å bidra til såkalt nitrering av for eksempel bjørkeallergener.

Det er behov for mer kunnskap om inneklimaets effekt ifht sykdomsutvikling og forløp ved etablert sykdom. Samtidig endres egenskapene ved norske bygg betydelig. Tettere hus, og endret ventilasjon bør følges tett av systematisk forskning. Ulike mer energieffektive og bærekraftige konstruksjoner og nye typer tekniske installasjoner bør følges tett av systematisk forskning. Dette inkluderer også rehabilitering av eldre bygningsmasse. Feltet krever tverr- og flerfaglig samarbeid.

Et eget forskningsprogram under Forskningsrådet som omhandler Miljøpåvirkning og helse, vil være viktig i denne programperioden.

Diagnostikk og forebygging ved etablert sykdom inkluderer å påvise og redusere ytre faktorer som forverrer sykdommen. Det er behov for kunnskap om organisatoriske forhold, utløsende mekanismer, helsefremmende påvirkninger og en lang rekke forhold – for eksempel:

- På hvilket nivå i helsetjenesten skal fødemiddelallergidiagnostikk finne sted?
- Ved etablert fødemiddelallergi: når og hvordan starte oral toleranseinduksjon?
- Hvilken rolle spiller miljøkjemikalier i luft/omgivelser for personer som har en astma, allergi- eller annen overfølsomhetsdiagnose?
- Hvilken rolle spiller inhalasjonspartikler (f. eks. veitrafikkstøv, annen luftforurensning) for personer som har en astma, allergi- eller annen overfølsomhetsdiagnose?
- Hvilken betydning har uteluft for helsetilstanden til en person med astma, allergi eller annen overfølsomhetsdiagnose? Hvor mye betyr trafikkforurensning, pollenvarsling, pollenfrie soner, allergenfrie miljøer? (matvarer/dyreallergener/pollen i eller ved skole)
- Hvilken betydning har arbeidsmiljøet for helsetilstanden til en person med AAO
- Hvilken betydning har inneklimaet hjemme (fukt og muggsopp, sosioøkonomiske forhold, utdanning/ barnehager og arbeidsliv) for helsetilstanden til en person med astma, allergi eller annen overfølsomhetsdiagnose?
- Hvordan skal man kartlegge fuktskader i bygg, og hvilke utbedringstiltak er mest virksomme? Hvordan skal balansen være mellom allergensanering og toleranseinduksjon?
- Hvordan evaluere effekten av opplæring om astma, allergi og andre overfølsomhetsreaksjoner hos personer som har slike tilstander?

Samhandling og bedre utnyttelse av helsetjenestens ressurser

Det er et behov for bedre **monitorering** av alle sykdomsgruppene ovenfor; det kan innebære re-evaluering av diagnoser og oppfølging av sykdomstilfeller. Det må tas stilling til hvilke metoder og retningslinjer som skal benyttes, hvor ofte oppfølgingen skal skje og på hvilket nivå i helsetjenesten.

Samhandling mellom primærhelsetjeneste og spesialisthelsetjeneste må forbedres. For AAO gjelder dette spesielt mellom lungeavdelinger, barneleger og fastleger. AAO- pasienter har relativt hyppige reinnleggelser, og det bør være et mål å redusere dette ved bedre samhandling. En strategi er å lære opp AAO- sykepleiere som en link mellom fastlegene og spesialisthelsetjenesten. Regionale sentra for AAO vil også være viktig for et bedret samarbeide.

En bør se på funksjonsfordeling/alvorlighetsfordeling av AAO mellom primær- og spesialisthelsetjeneste i forhold til pasientgrupper, kompetanse og helseøkonomi. Samhandling mellom forskjellige deler av spesialisthelsetjenesten vil kunne gi viktige bidrag innen forskningen. Norsk Gastroenterologisk Forenings Interessegruppe for Funksjonelle Gastrointestinale Lidelser arbeider med opprettelsen av et planlagt Nasjonalt Kompetansesenter for Funksjonelle mage-tarm-lidelser. Hvis et slikt senter kommer i stand, vil samarbeid med de regionale sentrene for AAO kunne gi viktige synergieffekter, ikke bare for forskning, men også for utredning og behandling av en stor pasientgruppe som i dag er nærmest forsømt.

Evaluering og implementering av forskningsresultater

Av **primærforebyggende råd** for AAO har det vært mange gjennom de siste 30-40 år. Disse har til dels vært gode og forskningsbaserte, for eksempel det å unngå aktiv og passiv røyking og det å unngå fuktskade i bolig (spesielt ved etablert astma, øvrige luftveissykdommer, astma og allergi i nærmeste familie og små barn i boligen).

For andre råd har det vært dels manglende kunnskapsgrunnlag, for eksempel det å unngå kjæledyr og det å unngå dundyner. Råd og anbefalinger som gis fra helsevesenet må derfor være godt vitenskapelig dokumentert, og må fortløpende kunne oppdateres i henhold til ny kunnskap. Helseforetakenes lærings- og mestringssentre (LMS) skal gi tilbud til personer og pårørende i AAO-gruppen på en ensartet måte i hele landet. De skal også utvikle kurs for kommunene slik at personellet i kommunene får hevet sin kompetanse og på den måten selv blir i stand til å gi oppfølging og opplæring av sine pasienter og brukere.

Alle forskningsprosjektene som er i gang eller som iverksettes i løpet av programperioden, bør sikres god oppfølging. Spesielt vil det være viktig å etablere egen oppfølging av de skisserte regionale AAO-sentrene og de nettverkene som er i ferd med å etableres. Det vil være naturlig å foreslå at følgeforskningen på dette området bør legges til et universitets- eller høyskolemiljø.

Oppsummert er det behov for:

- Forskning som kan bidra til redusert forekomst av AAO
- Forskning som kan bidra til bedre behandlingsresultater
- Forskning som kan bidra til god samhandling og bedre utnyttelse av helsetjenestens ressurser

Mulige tiltaksområder og tiltak

Som nevnt tidligere er det nødvendig å få på plass et bedre datagrunnlag og langt bedre oversikt over hele AAO-området. Deretter må det defineres mer presise mål og delmål. Tiltak kan utarbeides og implementeres når målsettingene er tydelig definert – og innenfor en del områder er det behov for mer forskning og intervensjonsstudier for å avdekke hvilke tiltak som gir effekt.

Faggruppene som har bistått med utarbeidelsen av Allergifrisk har foreslått at følgende tiltak *vurderes*. Noen av forslagene har god dokumentasjon og kan iverksettes umiddelbart, men andre bør prøves ut og evalueres som intervensjonsstudier.

Faggruppene har foreslått følgende tiltak/tiltaksområder:

- Økt samarbeid og samhandling mellom de myndighetsområdene som har ansvar for helse og de som har ansvar for energi- og utemiljøsektroene for felles kunnskapsutvikling og beslutningsunderlag for helsefremmende miljøtiltak
- Tiltak som gir økt ammefrekvens
- Tiltak som opprettholder høy naturlig eksponering for mat, dyr etc. for personer som ikke har en kjent allergisk lidelse eller en kjent overfølsomhet
- Tiltak som stimulerer til økt andel av barn som oppholder seg i «naturlige» miljøer for barn som ikke har spesiell astma-allergiproblematikk
- Tiltak for økt grad av regelmessig fysisk aktivitet som ledd i å styrke immunforsvaret.
- Tiltak for et sunnere og mer variert kosthold.
- Tiltak for redusert antibiotikabruk ved infeksjoner.
- Tiltak for å redusere andelen av befolkningen som røyker.
- Bidra til bedre inneklima for folk flest, men særlig i skoler, barnehager og på arbeidsplasser.
- Redusert eksponering for allergener eller andre faktorer som utløser en reaksjon eller bygge opp toleransen for allergenene der dette er mulig.
- Forbud mot utplanting av bjerketrær på offentlig tilgjengelige områder
- Tidsfrister hver sommer for gjennomføring av kantslått av hensyn til burotallergikere.

Forskningsprosjektet Prevent ADALL og annen internasjonal forskning på området vil om noen år kunne gi oss svar på om følgende tiltak bør iverksettes:

- Tiltak som gir økt andel av spebarn som får introdusert ulike matallergener i kosten fra 4 måneders alder
- Tiltak som bidrar til å styrke hudbarrieren hos spedbarn

4. BAKGRUNN

Dette kapitlet inneholder bakgrunn og begrunnelse for de strategiske valgene som speiles i programmets hovedsøyler

4.1 Økt motstandskraft mot astma, allergi og andre overfølsomhetsreaksjoner

Ved å øke motstandskraften vil vi kunne hindre at sykdom oppstår. I likhet med mange andre land i den vestlige verden, er allergiforekomsten i Norge stor. Mange studier i de senere årene har vist at omgivelser som er rike på et mangfold av mikroorganismer i barnets første leveår, vil redusere senere utvikling av allergiske lidelser. I forbindelse med økt urbanisering, har sped- og småbarns eksponering for mangfoldet og mengden av ulike mikroorganismer blitt betraktelig redusert.

Det ser ut som at immunsystemet kontinuerlig må eksponeres for ulike ufarlige bakterier og sopper gjennom hud, luftveier og mage/tarm-kanalen for å stimulere immunsystemet, inkludert de regulatoriske T-celler i tilstrekkelig grad til å utvikle en naturlig toleranse for miljøfaktorer.
For næringsmidler utvikles ofte en naturlig toleranse hos små barn som *har vært* allergiske - typisk for egg eller melk. For andre allergier er det større tendens til at allergien vedvarer. Ett behandlingsprinsipp for personer med allergi baserer seg på å endre immunsystemet til ikke å reagere på allergenene med allergisymptomer ved gradvis økende eksponering for det aktuelle allergenet inntil en viss mengde tolereres. Deretter fortsettes behandlingen inntil toleranse for allergenet er utviklet. Dette skjer i dag i stor grad for typisk pollenallergi eller alvorlig insektallergi (bi/veps), hovedsakelig ved hjelp av allergen-spesifikk underhuds- og sublingual immunterapi (tabletter som legges under tungen). Slik behandling forsøkes nå også for fødemiddelallergi i form av økende doser allergen som spises, men er ikke ennå i vanlig bruk. Denne type forskning er svært viktig for om mulig å ha også et behandlingstilbud til personer med alvorlig fødemiddelallergi.

Enkelte studier viser at økt toleranse til en viss grad også kan oppnås ved hjelp av mer uspesifikke midler så som Probiotika og sannsynligvis heller mer opphold ute i naturen enn mindre. (Probiotika = er

kosttilskudd som inneholder bakterier som forbedrer fordøyelse og helse, spesielt etter behandling med antibiotika eller cellegiftkur.)

Forskning har vist at kontinuerlig eksponering for så vel bakterier som andre allergener i matvarer og i omgivelsene er avgjørende for utviklingen av god helse og at forsøk på å redusere slike påvirkninger i stor skala kan være skadelig og svekke eller direkte hindre utviklingen av gode regulatoriske mekanismer. Det er synspunkter som dette som sammenfattes i *biodiversitetshypotesen.*

- Konsekvensen av denne kunnskapen er følgelig å revidere og presisere rådene til den del av befolkningen som ikke har astma, allergi eller annen overfølsomhetsreaksjon.

Særlig på to områder er det imidlertid dokumentert at det er riktig å opprettholde rådet om å unngå allergener. Barn og unge bør skjermes for passiv røyking og for fuktig inneluft/muggsopper. Begge faktorene bør rutinemessig tas opp av helsesøster.

4.2 Reduksjon i eksponeringen for reaksjonsutløsende risikofaktorer

Hver enkelt må i stor grad selv ta ansvar for å unngå miljøer hvor det er risiko for å utsettes for faktorer som gir reaksjoner. Samtidig kan og bør samfunnet legge til rette for at flest mulig kan navigere slik at de unngår eksposisjon. En avgjørende faktor er bedre matmerking som bidrar til at ingen uforvarende blir eksponert for noe som gir eller kan gi en reaksjon.

Det oppstår interessekonflikter mellom de som ikke er allergikere og som heller ikke har en kjent familiær disposisjon på den ene siden og de som er allergikere og/eller har en sterk familiær disposisjon på den andre siden: Hvor mye hensyn skal storsamfunnet ta til de som har den aktuelle lidelsen eller den kjente disposisjonen? Spørsmålet melder seg særlig i offentlige rom, ute som inne, f. eks. i hvilken grad skal man gjøre en hel skole fri for nøtter eller egg når det er ett barn på skolen som ikke tåler slike matvarer?

Utvikling og gjennomføring av tiltak forutsetter et bredt samarbeid med andre samfunnssektorer, og god informasjon til de med AAO.

4.3 Styrket diagnostikk, behandling og veiledning av enkeltpasienter og pasientgrupper

Veiledning av enkeltpasienter og pasientgrupper har stor betydning for effekten av så vel helsefremmende som forebyggende, diagnostiske og terapeutiske tiltak. Er ikke pasienten *med*, vil mange av tiltakene falle på stengrunn og således få redusert verdi.

God behandling basert på *tidlig og riktig diagnostikk* gir lettere sykdomsforløp, hindrer at tilstanden blir verre og forhindrer unødvendig behandling eller unødvendige restriksjoner. For akutt oppstått sykdom

eller akutte forverrelser, er det viktig å komme til med behandling tidlig. Igjen vil det her dreie seg om til dels spesifikke tiltak og dels om mer uspesifikke tiltak.

Behandlingstiltak vil dreie seg om:

- Allergen-spesifikk immun-terapi («Allergivaksinasjon»). Dette er spesifikk immunterapi der det gjennom munnslimhinnen eller ved injeksjon (subkutant eller direkte i lymfeknute) tilføres gradvis økende mengder av allergener for å redusere immunresponsen og derved øke toleransen. Dette er enda på forsøksstadiet når det gjelder matallergi.

- Pasienter med bjerkepollenallergi og reaksjon på matvarer som kryssreagerer med bjerkepollen, kan oppnå økt toleranse for disse matvarene ved spesifikk immunterapi mot bjerkepollen.

- Ved begynnende eksemoppbluss eller astmatisk eller allergisk reaksjon: «treff tidlig og treff hardt» med behandlingstiltak.

5. OPPFØLGING, ORGANISERING OG EVALUERING

Et så omfattende program som det her legges opp til, må sikres en solid evaluering. Ikke minst er dette viktig fordi en så stor del av arbeidet består i helsefremmende og forebyggende tiltak. Det å dokumentere effekter av slike tiltak er tradisjonelt vanskeligere enn å dokumentere effekten av behandlingstiltak. Som nevnt ovenfor vil det være avgjørende for å måle effekten av programmet at vi har gode grunnlagsdata. Programmets første år vil ha som mål å skaffe slike data. Når vi har skaffet disse grunnlagsdataene – kan vi sette oss klarere mål som kan oppnås gjennom dette programmet.

Helsedirektoratet minner også om kravet til oversikt i den nye folkehelseloven, § 5 *(Oversikt over helsetilstand og påvirkningsfaktorer i kommunen).*

Tallmaterialet må belyse hvordan tilstanden ute i befolkningen endrer seg over tid, hvordan eksponeringsnivåene endrer seg, hvordan ressurser til arbeidet fordeler seg og hvordan ressursene brukes.

Helsedirektoratet mener at en utenforstående instans, for eksempel en høyskole eller et universitet, bør få i oppgave å drive følgeevaluering av det programmet som blir bestemt. En midtveisevaluering vil være aktuell å foreta for eventuelt å kunne endre programmets retning.

Helsedirektoratet vil komme tilbake til den endelige organiseringen av arbeidet med nytt program når innholdet i programmet er vedtatt. Helsedirektoratet har trolig behov for en styringsgruppelignende innretning, for eksempel en forlengelse av dagens koordineringsgruppe. Som det fremgår av denne redegjørelsen, er det i nåværende strategiplan etablert flere referansegrupper. Helsedirektoratet vil se nærmere på strukturen som disse gruppene har. Gruppene bidrar i dag aktivt med sin erfaring og brede kompetanse. Gruppene er sammensatt med både sin faglige og sin brukerkompetanse.

Når innholdet i den nye planen synes klart, er det viktig at Helsedirektoratet er sikret den nødvendige finansieringen for å sikre programmets gjennomføring. Dette inkluderer også forskningsmidler. Anslått behov for forskningsmidler i 10 årsperioden vil være: 10 post doc årsverk pr. år (d.v.s. 2 årsverk ved hver Universitetsklinikk) som skal drive både klinisk og samfunnsbasert forskning, inkl. miljømedisinske tiltak.

6. VEDLEGG OG REFERANSER

6.1 Tidligere strategier, planer, prosjekter og tiltak på området astma og allergi

- Innstilling om plan for astmaomsorgen i Norge (1969), fulgte som vedlegg til nedenstående:

- Stortingsmelding 86, 1970/71: **Astmaomsorgen i Norge**

  Et samlet storting gikk inn for
  – **forskning på alle nivåer** + **kompetanseoppbygging og**

  – **undervisning + informasjon,**

  Følgende ble gjennomført:
  – **Epidemiologisk undersøkelse om astma (Amund Gulsvik)**

  – **Tiltak ved frivillige organisasjoner: Norges Røde Kors + en folkeinnsamling**

  Innstillingen var ment som en storsatsning på astma og allergi hos barn.

- **"Voksentoppen" ble åpnet i 1971.**

Tanken bak Voksentoppen senter for astma og allergi var nettopp å utvikle det til et kompetansesentrum og lærested for fagfolk kombinert med forskning. Beliggenheten ble valgt for å slippe luftforurensningen i Oslo. Voksentoppen ble internasjonalt kjent og aktet for sin tverrfaglige arbeidsmodell inkl. det som karakteriserer tertiærforebygging.
Av sykehuspolitiske grunner ble Voksentoppen nedlagt i august 2009 og de medisinske funksjoner flyttet til Rikshospitalet på Gaustad. Brukerne opplevde dette som en sterk reduksjon i tilbudet for en helhetlig ivaretaking av barn med astma og allergier.

- **Helsedirektoratets utredningsserie 6 -90: Retningslinjer for inneluft-kvalitet**

- **Helsedirektoratet 1991. Handlingsplan for Inneklima og helse**

- Hdir. utredningsserie 2-91: (182 sider)(Kjell Aas) ”**Handlingsplan for barn og unge med allergi/overfølsomhet, astma og andre kroniske lungesykdommer”.**

- 28 kapitler, 97 konkrete forslag om tiltak. Med omkostningsoverslag.
- Pasientrettede forebyggende og helsefremmende tiltak med konkrete forslag på områdene:
    - Miljøforhold
    - Helseopplysning og kommunikasjon
    - Kompetanseøkning
    - Organisering
    - Forskning

Det ble beskrevet tverrfaglige og tverretatlige tiltak i alle nivåer av et medisinsk og sosialt ”servicefilter”.

Denne utredningen var basis for allergi- og inneklima-satsningen i den følgende:

- Stortingsmelding nr. 37 (1992-93)**, ”Utfordringer i helsefremmende og forebyggende arbeid”**

Stortinget ber her regjeringen inkludere forebygging av astma, allergi og inneklimasykdommer blant hovedsatsings-områdene i det forebyggende og helsefremmende arbeid med følgende mål:

- Innen år 2002 skal samordnet planlegging og tiltak mot helseskadelig innemiljø sammen med helsefremmende kunnskap og atferd og tidlig intervensjon overfor de som rammes, føre til stopp i økningen av forekomst av astma og allergi hos barn under 7 år og til mindre sykelighet og bedre funksjon i alle aldersgrupper.

Fokusområdene i stortingsmeldingen forøvrig var psykososialt miljø, belastningslidelser og ulykker og skader. Inneklima /astma og allergi kom med som et fjerde satsningsområde.
Dette resulterte bl.a. i følgende rapporter og informasjonstiltak, bl.a. :

- **H.dir. veiledningsserie 4-95: ”Inneklima – en veileder for kommunehelsetjenesten”**
- **H.dir.: Rapport om astma, allergi og inneklimasykdommer (april 1996),**

- 6 departementer: **Handlingsplan 1993 – 1996. Handlingsplan for Godt inneklima i Norge.**
    - **Sammendragsrapport. Konsekvensanalyse av Handlingsplanen for Godt Inneklima i Norge 1993.**

- **Handlingsplanen Godt inneklima i Norge 1992 – 1996,** Sluttrapport, mai 1997.

• Handlingsplan: **"Forebygging av astma, allergi og inneklima-sykdommer 1998-2002»** – 7 departementer. Denne handlingsplanen ble ledsaget av:

- **"Faktarapport om astma, allergi og inneklimasykdommer"** (1998). Sosial- og helsedep.

Handlingsplanen ble fulgt opp med **«Statusrapport per 31.05.99. Handlingsplan for forebygging av astma, allergi og inneklimasykdommer 1998-2002».** Lignende oppfølginger ble foretatt 31.5.2000 og 31.5.2001 og 2003.

• **Stortingsmelding nr. 16** (2002-03) oppsummerte utviklingen etter Stortingsmelding nr. 37. Her ble særlig skade- og ulykkesforebygging satt på dagsorden, men ikke astma / inneklima.

• **"Konferanse om ny strategi for forebygging av astma, allergi og inneklimasykdommer"** –Kafé-dialog. (SHdir. August 2003)

• **Nasjonal strategi for forebygging og behandling av astma- og allergisykdommer (2008-2012)** (se også kapittel 6) (se også eget løst vedlegg)

Noen informasjonstiltak – offentlige

• **Helse- og omsorgsdepartementet/ Helsedirektoratet**

– **Forskrift om miljørettet helsevern i barnehager og skoler m.v. (1996) med veileder**

– **"Røykeloven" med informasjonskampanjer (2004)**

– **Fire informasjonshefter (2007-09) om innemiljø (samarbeid m. NFBIB)**

• **Folkehelseinstituttet (www.fhi.no)**

– **Inneklima i skoler og barnehager. Fukt og muggskader; mm. (2001)**

– **Luftkvalitet / Inneklimanormer / Inneforurensninger (2 utgaver) mm. (1991, 1998, revidert 2013)**

- **Statens Bygningsteknisk etat (BE)**

– **Hus og Helse prosjektet** – kurs – informasjon – byggebransjen (omarbeidet og revidert til hefte, men ikke fulgt opp med nye kurs)

- **SFT** (det daværende Statens forurensningstilsyn)

– Uteluftkvalitet, luftforurensninger, **forurensningsvarsler**

Informasjon – andre aktører

- **Voksentoppen åpen rådgivningstelefon** (nedlagt)
- **Rådgivingstelefon (inneklima, allergi) i 5 kommuner** (nedlagt)
- **NAAF (Norges astma og allergiforbund, www.naaf.no)**

– Rådgivning: inneklima, materialvalg, pollenvarsling, Matskolen

- **NFBIB (Norsk forum for bedre innemiljø for barn, www.innemiljo.net)**

– Elevenes rettigheter i skolen etter §9a

– Barnehagebrosjyre - informasjon

– Fire informasjonsbrosjyrer om innemiljø for H.dir. mm.

'Helserådet' rapport:

– Spesialnummer om inneklima: nr. 10/12 og 23/13

– Spesialnummer om matallergi, matintoleranse og andre overfølsomhetsreaksjoner på mat: nr. 20/12

– Spesialnummer om pollenallergi (Pollen og planter til besvær): nr. 8/13

- **Kunnskapsbanker på Internett om allergi/inneklima**

– Helsebiblioteket (www.helsebiblioteket.no) , Folkehelseinstituttet (www.fhi.no);

- **NAAF's nettsider, www.allergiviten.no ; www.inneklima.com mfl.**

Myndighetstiltak - skoler

- **Kunnskapsdepartementet / Utdanningsdirektoratet:**

Miljøgodkjenning av skoler. Spørreundersøkelser om oppfylling av krav til godkjennelse av skolers inneklima

– 2007 Barneombudet

- 2008 U.dir og H.dir
- 2009 H.dir
- 2010 H.Dir + fylkesmennene

- **Arbeidstilsynet**

- Røykeloven på arbeidsplasser
- Skoleprosjektet 2009 – påviste svikt i HMS for forsvarlig inneklima hos 50%

Resultater for skoler og barnehager

- **Flere spørreundersøkelser i skoler**

  - I 2010 var minst 32% ikke tilfredsstillende godkjent. I 2013 er 34 % av skolene ikke godkjent). På denne bakgrunn har Helsedirektoratet i samarbeid med Utdanningsdirektoratet og Arbeidstilsynet i 2014 startet et fylkesvis opplæringsprogram, en kampanje kalt «Krafttak for et bedre miljø ved skolene i landet – Hva skal til for å få alle skolene godkjent?»

- **Hva med barnehagene?**

  Tilsyn og nye krav er pålagt, men bare delvis fulgt opp

Forskning

- Foreslåtte tiltak i 1991 (pkt. 57-60)

Forskningen på inneklima og allergi skulle legges til universitet og høyskoler samt til Voksentoppen. Forskningen skulle gis høy prioritet og rammebevilgninger svarende til viktigheten.

- **Norges forskningsråd**

- **"Inneklima og helse" (1995-2000).** Stor interesse. Fukt og mugg - prosjekter ble underfinansiert og større prosjekter ble ikke realisert

- **Byggforsk / Sintef**

- Omfanget av inneklimaproblemer i Norge (1992)
- Bedre innemiljø i sykehus (Haukeland) 1995

- Inneklima i barnehager / Betong i bygninger – konsekvenser for inneklima – Forprosjekt 1996.

- **Div. inneklimaprosjekter i Trondheimsområdet; HUNT**
- **Folkehelseinstituttet**
  - **Barn og innemiljø**, oppfølging over 10 år; **matallergiforskning**

- **Andre**
  - **Rogalandsforskning**: inneklima og prestasjoner i skoler
  - **Miljø- og Barneastmaprosjektet, OUS / tidl. Voksentoppen /Fhi**
  - **Miljø- og yrkesmedisinske avdelinger**: Yrkesallergier (hud og luftveier)

A 10 year asthma programme in Finland: major change for the better

T Haahtela, L E Tuomisto, A Pietinalho, T Klaukka, M Erhola, M Kaila, M M Nieminen, E Kontula and L A Laitinen

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ASTHMA

A 10 year asthma programme in Finland: major change for the better

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Background: A National Asthma Programme was undertaken in Finland from 1994 to 2004 to improve asthma care and prevent an increase in costs. The main goal was to lessen the burden of asthma to individuals and society.

Methods: The action programme focused on implementation of new knowledge, especially for primary care. The main premise underpinning the campaign was that asthma is an inflammatory disease and requires anti-inflammatory treatment from the outset. The key for implementation was an effective network of asthma-responsible professionals and development of a post hoc evaluation strategy. In 1997 Finnish pharmacies were included in the Pharmacy Programme and in 2002 a Childhood Asthma mini-Programme was launched.

Results: The incidence of asthma is still increasing, but the burden of asthma has decreased considerably. The number of hospital days has fallen by 54% from 110 000 in 1993 to 51 000 in 2003, 69% in relation to the number of asthmatics (n = 135 363 and 207 757, respectively), with the trend still downwards. In 1993, 7212 patients of working age (9% of 80 133 asthmatics) received a disability pension from the Social Insurance Institution compared with 1741 in 2003 (1.5% of 116 067 asthmatics). The absolute decrease was 76%, and 83% in relation to the number of asthmatics. The increase in the cost of asthma (compensation for disability, drugs, hospital care, and outpatient doctor visits) ended: in 1993 the costs were J218 million which had fallen to J213.5 million in 2003. Costs per patient per year have decreased 36% (from J1611 to J1031).

Conclusion: It is possible to reduce the morbidity of asthma and its impact on individuals as well as on society. Improvements would have taken place without the programme, but not of this magnitude.

The last 10 years have been a golden period for asthma guidelines, both internationally and nationally.[1–11] These guidelines aim at improving the standard of asthma care, but the current level of asthma control still falls short of published guidelines, even in Europe.[12 13] The key question has been implementation of the best practice at the various levels of health care. Successful management depends on promoting adherence of both healthcare providers and patients to treatment.[14 15]

In the early 1990s the Ministry of Social Affairs and Health in Finland (population 5.2 million) recognised asthma as an important public health issue and set up a national programme lasting from 1994 to 2004 to improve asthma care and limit the projected increases in costs.[16] The Finnish programme is comprehensive and reaches deep into the structures of health care. The first results of the programme were reported at the end of 2000.[17] The present paper summarises the results of the whole programme period from 1994 to 2004.

METHODS

Working strategy and implementation

The steering committee of the programme set goals and measures, and planned activities both for adults and children.[16] The main goal of the 10 year programme was to lessen the burden of asthma on individuals and society.

Measures to achieve the goals were as follows:

- early diagnosis and active treatment;
- guided self-management as the primary form of treatment;
- reduction in respiratory irritants such as smoking and environmental tobacco smoke;
- implementation of patient education and rehabilitation combined with normal treatment, planned individually and timed appropriately;
- increase in knowledge about asthma in key groups; and
- promotion of scientific research.

The programme was run by the Finnish Lung Health Association (Filha), a non-governmental organisation (expert NGO, www.filha.fi) and employed one pulmonologist. Overall, the direct extra cost of the programme was J0.65 million including J125 000 from the Ministry of Social Affairs and Health who gave their political commitment to

Table 1 Stepwise educational sessions and target groups during the 10 year programme organized by Finnish Lung Health Association (Filha) and other professional bodies

Step	No of sessions	No of participants
(1) Pulmonary and paediatric hospital units	100	5300
(2) Primary and secondary care professionals	237	3700
(3) All healthcare professionals	450	25500
(4) Regional paediatricians and primary care professionals (mini-programme)	25	1300

Table 2 Facilities and knowledge of asthma care in Finnish health centres in 2000[20]

Facility/knowledge	Proportion of health centres (%)	
Peak flow meters available	100	
Guided self-management used	98	
Inhaled corticosteroid as first line medication	97	
Spirometry available	95	
Local asthma-responsible person designated		
Nurse	94	
General practitioner		83
Regional asthma programme available	79	
Diagnosis of adult asthma in health centre	77	
At least annual follow up visit recommended	75	
Asthma education arranged for professionals (mean 3.2 sessions/centre in 2 years)	71	

the programme. The intervention was managed by integrating the tasks into the everyday practice of healthcare staff. Most of the activities were part of the clinicians' and administrators' routine work.

The programme obtained broad commitment from Finnish health care. For instance, a 1998 survey of chief physicians showed that 90% had changed their asthma practices in their clinics based on the programme.[17] International adherence of doctors to the guidelines has been considerably lower.[14] Of the 21 Finnish hospital districts, 65% have also launched regional programmes.

The key to implementation has been the network of local asthma coordinators (one physician and at least one nurse) in each Finnish healthcare centre (n = 271). Two hundred local asthma-responsible physicians and 580 asthma-responsible nurses currently ensure the quality and continuity of asthma management in primary health care. Specialists in hospital based pulmonary and paediatric units have been responsible for regional cooperation, including developing and updating the referral and treatment network and regional guidelines.

The programme has been enlarged twice. In 1997 nearly all Finnish pharmacies were included in the Pharmacy Programme. The Association of Finnish Pharmacies created a network of 695 asthma pharmacists in local pharmacies and started their continuous training. In 2002 a Childhood Asthma mini-Programme was launched. This consisted of practical checklists including (1) a good referral letter to a specialist, (2) a reply letter from the specialist to the general practitioners (GPs) and to the parents, (3) a structure for follow up visits, and (4) a self-management form to be individualised for each patient. Asthmatic children had been almost exclusively under the care of paediatricians, but the role of GPs and primary care had to be strengthened.

Regional education

There were four main educational steps. All State Provincial Offices were informed of the objectives of the programme and Filha organized (together with hospital pulmonary and paediatric specialist units) half-day educational sessions. The regional specialist units in turn invited the local primary care coordinators to attend these sessions (table 1).

Patient organisations (NGOs: the Allergy and Asthma Federation and the Pulmonary Association HELI) have had a major impact in direct patient counselling and distributing free of charge booklets, videos, and CD-ROMS concerning asthma, allergy, smoking, indoor air quality, and ambient air pollution. Patient organisations and pharmaceutical companies have financially supported a major part of the educational activities but had to follow the general principles of treatment strategies and self-management guidelines set up for the programme.[16–18]

A summary of the activities of the Finnish asthma programme from 1994 to 2004 is shown in the online supplement available at http://www.thoraxjnl.com/supplemental.

RESULTS

Primary care

Primary care chief physicians in northern Finland (n = 58, response rate 78%) were surveyed by questionnaire in 2000.[19] They reported that knowledge and facilities to examine asthma patients were good in 84% of the healthcare centres; 70% of the centres had arranged asthma education staff meetings during the previous 2 years. A regional asthma physician acted mainly as a consultant to other GPs and coordinated the work with regional specialists. Asthma nurses gave most of the patient education and served as contacts for patients.

During 2000 and 2001 the asthma coordinating physicians (n = 248) were interviewed regarding their facilities and knowledge in 91% of the health centres.[20] The organisation and resources for asthma care were well established (table 2). Asthma nurses were surveyed with regard to their practices in 2004 (n = 431, response rate 73%). In 92% of the health centres patients were recommended to visit an asthma nurse after a scheduled physician visit, and this was an organised activity in 56% of the health centres (A Pietinalho, personal communication, 2005).

Communication between primary and specialist care

In 2004 regional adult asthma guidelines were available in 79% of the 21 hospital districts (in 52% also on their websites); 48% also had regional guidelines for children on their websites. For example, in Hyvinkää, a southern Finland hospital district (population 160 000), the regional guidelines were launched in 1998. The results of the implementation were evaluated before the launch (in 1997, 366 patients) and after (in 1999, 280 patients).[21] A major change occurred towards better use of specialist services. Asthmatics stayed in specialist care for shorter periods (2.3 years before, 1.3 years after) and specialists took care of those with more severe asthma. Guided self-management was used more often (36% v 46%) and patient satisfaction had risen from 65% to 75%.

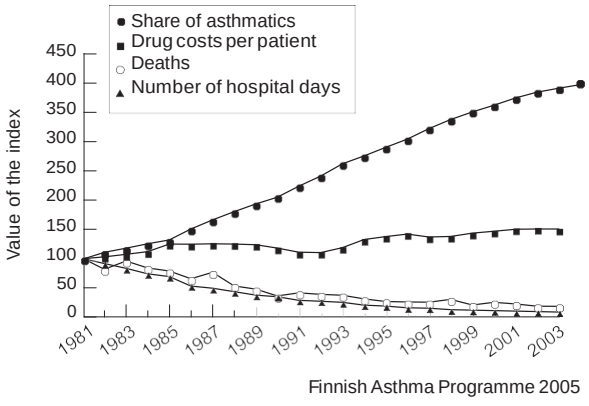

Figure 1 Increase in number of asthmatic patients entitled to special reimbursement for their drug costs, increase in drug costs per patient, decrease in death rate, and decrease in hospital days due to asthma. Numbers are relative changes after 1981 (index, 1981 = 100).

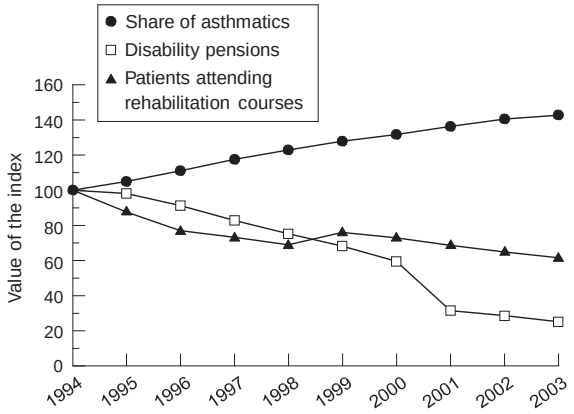

Figure 2 Increase in patients entitled to special reimbursement for their drug costs, decrease in patients on disability pensions, and decrease in patients attending rehabilitation courses for asthma. Numbers are relative changes after 1994 (index, 1994 = 100). Data from Social Insurance Institution.

Regular check-up visits also increased. In Southern Ostrobothnia (population 190 000) 26% of patients in 2000 and 48% in 2004 had made a check-up visit to their primary care physician during the previous year (L E Tuomisto, personal communication).

Pharmacies

The pharmacy programme has reached 94% of the Finnish pharmacies. In 2004 pharmacists provided patients with written or oral information on ''preventers'' and ''relievers'' during 98% of their purchases of asthma drugs.[22] Instructions on inhalation technique was provided to 98% of new asthmatics, and to 34% of others. The inhalation technique was actually checked for 53% of new asthmatics and for 12% of the others.

In the pharmacy surveys, in 1998 less than 80% of patients purchasing asthma drugs reported that they had their ''own'' asthma doctor, but in 2004 this proportion was as high as 95%.[23] Responsibility for care had been shifted to primary care, which was one of the main aims of the programme: 73% of adult asthmatics in 2000 had a GP as their asthma doctor; the figure was still low (17%) for children.[24 25]

Hospital admissions

The number of hospitalisation days began to decrease before implementation of the programme, but is still falling. In 1993, a year before the programme was launched, the number of hospitalisation days due to asthma was around 110 000 (271/100 000 patients). In 2003 this number had fallen to around 51 000 (120/100 000 patients). The reduction in absolute figures was 54%, and 69% in relation to the number of asthmatics.

For children, hospital admissions increased from 7.3 per 1000 in 1976 to 20.2 per 1000 in 1995. A remarkable 5.3-fold increase occurred in children aged ,5 years (2.6 per 1000 in 1976, 13.8 per 1000 in 1995).[26] After 1995 the admission rate turned downwards. In 1999 significant regional variation indicated differing practices for hospitalisations of children because of exacerbations. In the youngest age group hospitalisations varied from 3.1 to 7.4 per 1000 children).[27]

In 1981 the Finnish Social Insurance Institution (SII) recorded 49 300 asthmatics entitled to special reimbursement for their drug costs. In 2004 this figure had increased fourfold to 212 000. In relation to the number of patients receiving special reimbursement—that is, the real at-risk population—the number of hospital days in 2002 was only 10% of that in 1981 (fig 1). In comparison, hospital days due to chronic obstructive pulmonary disease (COPD) during the period from 1993 to 2003 increased by 5%.[28]

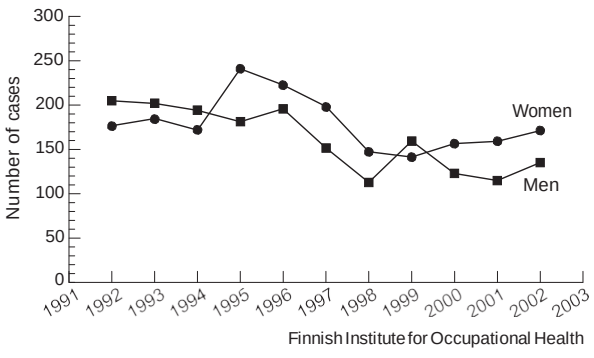

Figure 3 Registered cases of occupational asthma in Finland, 1992–2002.

Mortality

The absolute number of deaths fell from 123 in 1993 to 85 in 2003 (fig 1). As a proportion of patients with registered asthma, the respective rates were 0.91/1000 in 1993 and 0.41/1000 in 2003. From 1976 to 2003 a total of 27 deaths occurred among those under 20 years of age, with only 10 between 1990 and 2003 (annual death rate 0–0.35/100 000).

Emergency visits

In Pirkanmaa hospital district (population 450 000), emergency visits due to asthma decreased in adults by 24% from 1995 to 2003 and by 61% in children (official registry of Tampere University Hospital).

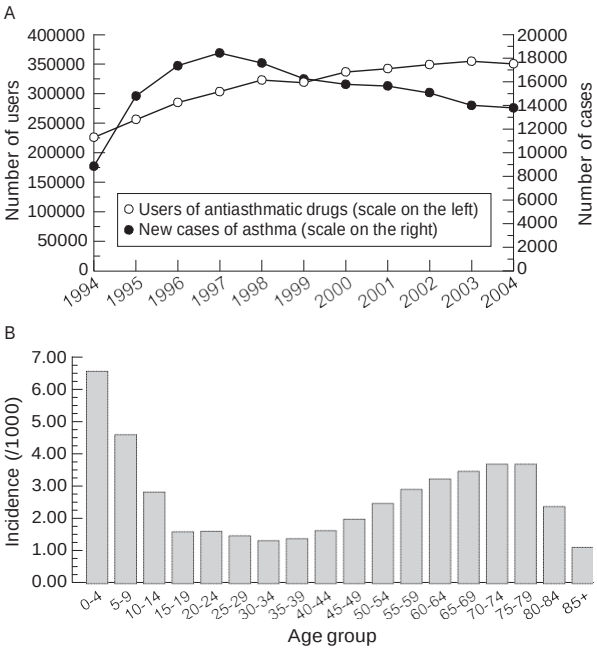

Figure 4 (A) Number of new patients entitled to special reimbursement for their drug costs from 1994 to 2004, and all users of anti-asthmatic drugs from 1994 to 2004 (not only those receiving special reimbursement for persistent disease). (B) Incidence of asthma patients (%) according to the special reimbursement register in 2004 by age group. Data from Social Insurance Institution.

Disability and daily allowances

In comparison with musculoskeletal or cardiovascular diseases or mental disorders, asthma is an uncommon cause for work disability. In 1993, 7212 patients of working age (9% of all asthmatics) received disability pensions from the SII compared with 1741 in 2003 (1.5%). The absolute decrease was 76% and, in relation to the number of asthmatics, 83% (fig 2).

Daily allowances paid by sickness insurance for asthma decreased by 27% from 1993 to 2003. Compensation was paid for 145 200 lost days in 1994 (2966 sickness periods) and for 105 700 days in 2003 (1920 sickness periods). The respective costs were J5.2 million in 1993 and J3.9 million in 2003. These figures include only those involving at least 10 day absences from work, those days for which allowances are paid.

Rehabilitation

Between the years 1994 and 2004, the number of patients attending adaptation training and rehabilitation courses for asthmatics organised by the SII (the major financer of rehabilitation) fell 57%, from 2758 to 1181 (fig 2).

Occupational asthma

Finland has strict legislation for occupational diseases, and all verified cases are registered. The number of cases of occupational asthma decreased in the 10 year period from about 400 to 300 per year (fig 3). This favourable trend is largely due to the long term active work of the National Institute of Occupational Health. In a Finnish population based follow up study, the proportion of cases attributable to occupation among 50 000 incident asthma cases was 29% (95% CI 25 to 33) for men and 17% (95% CI 15 to 19) for women, indicating that the effect of work is larger than generally assumed.[29] No comparable data are available from other countries.

Medication

In 1987 a nationwide health survey showed that only one third of Finnish asthma patients used inhaled steroids.[30] A major change has taken place since. Both in 2001 and 2004, over 85% of patients purchasing asthma drugs from pharmacies used inhaled steroids daily.[23]

According to SII registers, in 1993 the number of patients with asthma entitled to 75% reimbursement was around 135 500, of whom about 19 000 (14%) were children. In 2004 the total number was around 212 000 (a 56% increase), of whom 28 500 (13%) were children—a 50% increase. The number of registered new asthmatics increased steadily until 1997, since when it has been declining (fig 4A).

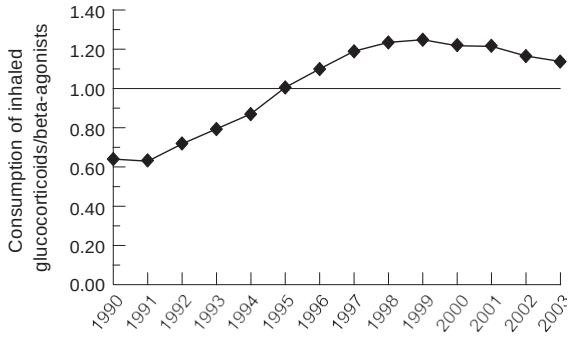

Figure 5 Ratio of consumption of inhaled corticosteroids and b_2 agonists from 1990 to 2003 in defined daily doses (ddd/1000 inhabitants/day). A combination of steroid and b_2 agonist was added to the prescriptions for both b_2 agonists and corticosteroids. Data from National Agency for Medicines.

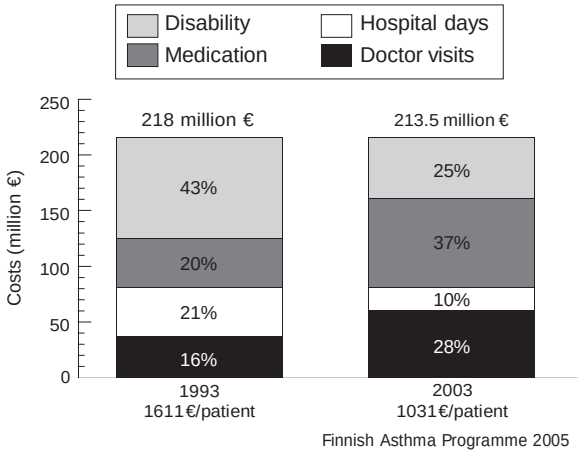

Figure 6 Direct annual costs of asthma (medication, hospital days, doctor visits) and compensation for disability pensions and days off work in Finland, 1993 and 2003. The gross national product in Finland was J19 809/inhabitant in 1993 and J27 585/inhabitant in 2003 (index year in all calculations 2003). Data from Social Insurance Institution.

The age related incidence of new registered asthma cases shows two peaks: a high peak among small children and another smaller peak among the elderly (fig 4B). Both peaks are slightly confounded, the former by overdiagnosis of asthma in infants and the latter by patients with COPD which, in the older age groups, accounts for about 5% of all patients entitled to reimbursement.

In another SII register established in 1994, prescriptions of asthma drugs increased steadily in the 1990s, but this trend slowed in the early 2000s and turned downwards during more recent years (fig 4A).

In 1995, Finland was the first Nordic country to reach a ratio of 1.0 for defined daily doses (ddd) of inhaled corticosteroids to those of b_2 agonists (fig 5). The use of combination inhalation preparations (salmeterol/fluticasone and formoterol/budesonide) has grown rapidly which has caused an increased use of b_2 agonists, even among those with mild asthma. This ratio has therefore again been approaching 1.0. A shift was promoted from metered dose inhalers to dry powder inhalers because of the foreseen international ban against CFC (freon) propellants. In 1993 dry powder inhalers comprised 29% of the total number of inhalers sold compared with 84% in 2003.

Of the nearly 50 chronic diseases which entitle the patient to special reimbursement, asthma was the second highest at the end of 2004, with only hypertension ahead of it. In children, asthma was by far the most common disease.

Smoking

From 1994 to 2004, smoking among Finnish men (28–27%) and women (20%) remained essentially unchanged.[31] Adolescents (age 14–18) smoked slightly more in 1996 (24%) than in 2004 (22%).[32] Asthmatics smoked as much as others from 1997 to 1999 in the Hyvinkää region (22–24%).[21]

In 1994 smoking was prohibited in all workplaces. The proportion of employees exposed to environmental tobacco smoke during working days decreased from 71% to 21% between 1994 and1998, and exposure to tobacco smoke for more than 4 hours a day from 33% to 3%.[33]

In a Finnish population based incident case-control study (521 cases, 932 controls) the risk for asthma was significantly

Table 3 Changes in asthma management during the programme

	1993	2004
Primary care		
General practitioner	Asthma suspicion referred to specialist without lung function tests Infrequent follow up visits Prescriptions renewed without check up	Diagnosis of asthma by GP Short specialist consultation as needed Anti-inflammatory treatment started without delay Easy access to evidence based guidelines and local treatment chains Annual follow up visits
Nurse	Rarely spirometry measurements made or peak flow values followed	Daily spirometry measurements Routine guidance in peak flow measurement and use of inhalers Patient centred asthma education with written action plan Annual follow up visits
Specialist care		
Adults	Diagnosis of asthma Most follow up visits Emergency care	Only a portion of new diagnoses Follow up of severe cases only Part of emergency care
Children	Diagnosis, treatment, follow up of all childhood asthma Inpatient treatment of acute asthma	Diagnosis of childhood asthma Treatment, follow up of preschool asthma Inpatient treatment of acute asthma
	1997	2004
Pharmacies		
Asthma coordinators	No actively organised role in asthma care	Active guidance in use of preventers and relievers; guidance in inhalation technique Networking with local health care

higher both among current smokers (adjusted odds ratio (OR) 1.33) and ex-smokers (adjusted OR 1.49) than among non-smokers.[34]

Costs

Costs attributable to asthma in Finland have decreased despite the substantial increase in the number of asthmatics (fig 1). In 1993, the year before the launch of the programme, the total direct costs from asthma and work disability were around J218 million (J1611 per patient), these sums being corrected by the inflation rate (fig 6). Ten years later the total costs of J213.5 million had decreased 2%, but costs per patient (J1031) had decreased as much as 36%. We can only speculate on the increase in total costs without the programme. If the costs per patient in 2003 had been the same as in 1993, total costs would have amounted to J341.5 million (potential saving J128 million for 2003). Development in health care and improved treatment would, however, have saved some costs even without the programme.

In 1993, sales of anti-asthmatic medicines in outpatient care were J44 million (20% of total costs), but in 2003 this share almost doubled to J79 million (37%). The annual cost of medication per patient with special reimbursement—that is, persistent asthma requiring regular treatment—was 1.8 times higher in 2003 than in 1993. This growth is causing concern and is mainly due to the increasing use of steroid/b_2 agonist combination preparations. The change to dry powder inhalers has also increased costs.

DISCUSSI ON

Did we achieve the goals?

The programme was aimed for the period 1994–2004. The changes in asthma management are summarised in table 3. We have been able to lessen the burden of asthma considerably and halt the increase in cost. The worrying trends are still the high incidence of asthma and growing drug costs. The preset goals were achieved as follows.

Goal 1: Recovery of as many patients as possible with early asthma

The number of children and adults with new special reimbursement for drug costs reached a turning point in 2001 and is decreasing. The asthma epidemic in Finland is still ongoing[35] but may have reached its peak, as has been suggested in some other Western countries.[36 37] Moreover, many patients who previously received entitlement to special reimbursement for a restricted period may no longer need it after successful initial treatment.

Goals 2 and 3: Patients should feel well and their abilities should correspond to those usual for their age. Decline in percentage of patients with severe and moderate asthma from 40% to 20%

Several indicators show that the proportion of patients with severe complications has substantially decreased, as have physical limitations. The absolute numbers for hospitalisation days, disability pensions, allowances for days off work, and need for rehabilitation have all decreased 30–50% and, in relative terms, even more.

Goal 4: Decrease in number of days hospitalised by 50%

The number of days hospitalised has fallen by 56% from 110 000 in 1993 to 51 000 in 2003, and in relation to the number of asthmatics by 70%. The trend is still downwards.

Goals 5: Reduction in annual costs per patient by 50%

When compensation for disability, drugs, hospital care, and outpatient doctor visits are taken into account, costs per patient have decreased 36% and, if related to the increase in gross national product, by 50%.

Lessons learned

To tackle common diseases like asthma requires a multidisciplinary action programme. This programme should include an operational plan for implementation and follow

up. Effective strategies involve multiple methods, decision support systems, and interactive education.[38] A broad commitment by the healthcare system and society is mandatory and should be sought at an early stage. The Finnish Ministry of Social Affairs actively supported the programme and acknowledged that asthma can be effectively detected and treated early.[39–41] The steering group should be small (not more than 7–10 people), but it should comprise state officials, key experts, nurses, pharmacists, and patient organisations. Political commitment must be confirmed also at the regional level: state officials organised, in cooperation with the expert NGO (Filha), interactive sessions with the regional pulmonary and paediatric units. The regional specialist groups created a network of contact persons in local health centres as well as regional treatment guidelines and referral chains. The essence of long term success is to keep alive the network of contact persons, GPs, nurses, and pharmacists.

As the programme shifted its focus from maintenance treatment to early detection and prevention of exacerbations, the pulmonologists and paediatricians had to rethink their practices in order to ensure functioning regional treatment chains. The patients usually first contact their health centres regarding symptoms.

The shift in care from specialist to primary health providers has taken place over the whole country. Children are still mostly cared for by paediatricians; specialist work has also improved. For example, in a middle sized Finnish hospital in 1994, 16% of new asthma diagnoses were made during the first visit compared with 42% in 2001 (L E Tuomisto, personal communication).

Small clinical improvements have a significant impact. For example, instructing primary care staff how to use a 2 week peak expiratory flow follow up and when to try a course of an inhaled steroid energised their work considerably. Furthermore, systematic teaching of the use of spirometry has proved useful. These simple means have essentially improved case identification and early intervention. Co-morbidities of asthma like rhinitis, as well as allergic factors causing disease persistence, have also been in the educational focus.

Asthma treatment is drug centred and the programme recommended a simple medication regimen[16] which has since been slightly modified. In recent years the decrease in new asthma patients entering the special reimbursement register probably indicates earlier and more effective intervention resulting in less persistent disease.

When purchasing drugs, the asthma patient has an important contact with a pharmacist. Along with the pharmacy programme, asthma pharmacists began instructing patients in the use of preventers and relievers (noticing excess purchases of relievers) and on the inhalation technique. Peak expiratory flow measurements have also been a topic of instruction in some pharmacies. Pharmacists have been highly motivated to follow the new initiatives.

One important and evidence based strategic choice was guided self-management.[42] In one district the use of guided self-management increased in 2 years from 36% to 46%, accompanied by improved patient satisfaction.[21]

Approximately 70% of all asthma is mild and may require only intermittent drug treatment.[43] However, in both mild and more severe asthma, guided self-management is essential in preventing prolonged symptoms and exacerbations. Understanding and partnership are more important than compliance.[44] The essential principles in asthma medication for adults and school-aged children are shown in Appendix 1.

Childhood asthma requires special consideration and a mini-programme for children was included in 2002. An electronic, easy to fill in and print self-management form is serving as the written (and readable) action plan. The developed checklists for referral letter, diagnostic work, and follow up are helping in both primary and secondary care.

This kind of programme cannot be effective without organised follow up and feedback, but even these are not enough. A rigorous evaluation plan is necessary in every large development programme. This was not fully acknowledged in 1994 when the Finnish initiative was taken, and caused problems in assessing the true impact of the programme.

Financial resources are necessary to start up and monitor the programme, but the two key words for success are ''motivate'' and ''organise''. Once the local work starts, it has its own dynamic which spreads to other regions who do not want to perform less well.

Focal points for the future

- The role of asthma nurses should be strengthened and made more independent. Educated nurses could tend to most routine check ups.
- Guided self-management should be further encouraged and a written action plan demanded. An electronic asthma follow up sheet has recently been developed for nation-wide use.
- Clinical work requires handy tools to detect and monitor the inflammatory component of asthma. One recent innovation is a portable device to measure exhaled nitric oxide.
- Asthma in children under the age of 5 is often difficult to diagnose and, for treatment, specific guidelines may also be necessary to avoid both undertreatment and over-treatment.
- Anti-smoking work is still essential among asthmatic subjects. National smoking cessation guidelines have recently been published.[45]
- The combination preparations of inhaled steroids/b_2 agonists may have improved the overall asthma control slightly but at a high cost. They are therefore not recommended as first line drugs.[18] The unnecessary increase in drug costs should be halted.
- The Finnish government promotes a common electronic database for all healthcare providers to be in action in 2008. In the asthma treatment chain this database would allow, for example, better identification of patients in need of emergency visits and monitoring of prescriptions in local pharmacies.

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A summary of the activities of the Finnish asthma programme from 1994 to 2004 is shown in the online supplement available at http://www.thoraxjnl.com/supplemental.

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APPENDIX 1: ESSENTIAL PRINCIPLES IN ASTHMA MEDICATION FOR ADULTS AND SCHOOL-AGED CHILDREN

Treatment is always tailored to patient needs. These principles have been slightly modified since 2001.[17]

Principle 1: Start effective anti-inflammatory treatment early, win the patients confidence, and improve the outcome

- Get the disease under control with a moderate to high dose of inhaled steroid—for example, for 4 weeks. Adjust dose according to the need for a reliever, a rapid acting b_2 agonist.
- Step down dose to maintain the result, and further down to identify the lowest dose to control symptoms and maintain lung function.
- Check inhalation technique and treatment adherence if treatment is insufficient.

Principle 2: Treat according to disease severity

- Intermittent symptoms. Inhaled steroid, for example in 4 week courses, rapid acting b_2 agonist as needed.
- Mild, persistent symptoms. Inhaled steroid regularly, dose may vary. Rapid acting b_2 agonist as needed. Leukotriene modifier as a possible alternative to inhaled steroid, which is usually more effective.
- Moderate, persistent symptoms. Inhaled steroid and long acting b_2 agonist from two separate inhalers or from a single inhaler (combination preparation) regularly. Dosage

6.3 Det finske allergiprogrammets midtveis evaluering

13.12.13 Oslo/**Confidential**

Five years on the new allergy track –

The Finnish Allergy Programme 2008-2018

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Abstract

BACKGROUND:

There are no nationwide, comprehensive public health programmes on allergic disorders with set goals and systematic follow-up. The Finnish Allergy Programme 2008-2018 is based on the concept that the so called allergy epidemic in modem, urban societies is caused by impaired development of tolerance.

METHODS:

The 10-year implementation programme aimed to endorse allergy health and reduce burden of allergies both at the individual and societal levels. The main goals were set to (1) prevent development of allergic symptoms, (2) increase tolerance against allergens, (3) improve diagnostic quality, (4) decrease work-related allergies, (5) allocate resources to severe allergy and asthma, and (6) decrease overall costs due to allergic diseases. The indicators for the goals were numeric, e.g. asthma emergency visits should drop 40% in 10 years. For each of the goals, specific tasks, tools and outcome evaluation were defined.

RESULTS:

The first 5-year results of the Finnish Programme indicate a major change for the better. Diagnostic quality has improved as 15 public allergy testing centres have been audited and certified, in many areas food allergy diets in day-care centres and schools have decreased by 20-25%, occupational allergies have decreased by 30-50%, and asthma emergency visits and hospital days have halved. In 2007-2011 direct allergy costs and costs of disability pensions reduced from € 374 to € 357 million (-5%). Asthma costs were 65% of all costs and reduced from around € 250 to € 227 million (-9%), respectively.

CONCLUSIONS:

The case Finland shows major improvements can be achieved with simple means, if the society is committed to reduce the burden. It is time to revisit allergy paradigm, and act, when allergic individuals are becoming a majority of Western populations and their numbers are in rapid increase worldwide.

Key words: allergy programme, atopic eczema, anaphylaxis, asthma, immune tolerance, public health programme, rhinoconjunctivits, self-management

Introduction

The dogma of general allergen avoidance has not proved effective in halting the 'allergy epidemic', although avoidance will stay in the treatment armamentarium of individual patients. Restoring and strengthening tolerance might be the key to a better immune balance at population level and should be more in focus. Understanding the mechanisms of tolerance paves also the way from treatment to prevention, allergy health and better public health altogether.

The prevalence and burden of allergic diseases has grown in Finland during the last 50 years, similarly to many other industrialized and urbanized countries (1). Although the origin of allergy remains unresolved, increasing body of evidence indicates that modern man living in urban built environment is deprived from environmental protective factors (e.g. soil micro-organisms) that are fundamental for normal tolerance development. Reduced contact of people with natural, biodiverse environments and changes in nutrition may adversely affect the human commensal microbiota and its immunomodulatory capacity. Recent results from North Karelia have prompted the so called biodiversity hypothesis, which enlarges the hygiene- and microbial deprivation hypotheses by taking into account the interrelationships of three DNA compartments: human cells, skin-mucosal microbiomes and environmental microbiomes (2-5). Immune system seems to be compromised to make difference between danger and non-danger (allergy) or self and non-self (autoimmune diseases). Immune dysfunction can lead to inappropriate inflammatory responses and clinical disease. To stop this, the role of protective factors must be understood better.

In Finland (population 5, 4 million), a 10-year Allergy Programme 2008-2018 (AP) was taken to reduce burden of allergies both at the individual and societal level (6, 7). This was done by aiming to increase both immunological and psychological tolerance and change attitudes to support health instead of medicalising common and mild symptoms. Severe forms of allergy were in special focus, e.g. asthma attacks were prevented proactively by improving disease control with the help of guided self-management. Networking of allergy experts with primary care doctors, nurses and pharmacists was regarded the key for effective implementation. Non-governmental organizations (NGOs) were encouraged to start a campaign to increase allergy awareness and knowledge among patients and general public.

Six main goals were set and for each goal specific tasks, tools and evaluation methods defined. One recent tool is practical recommendations for childhood allergies (8).

Here, we summarize the main methods for implementation of AP and give interim results at 5 years.

Methods

Planning and testing the messages

The early steps of the Allergy Programme were taken already in 2004 by the initiative of a non-governmental organization, Allergy & Asthma Federation to the Ministry of Welfare & Health in Finland **(Fig. Sl,** in Supplementary Material). Under the surveillance of National Institute for Health & Welfare (NIHW) an expert group evaluated the evidence of allergy prevention and management. In 2006 a report of immune tolerance and how to improve it was published Finnish, This was followed by the work of a partly different expert group to create an action AP, which was launched in 2008. The organizational structure ofthe work is given in **Fig. S2** (in Supplementary Material). The process was coordinated and followed by an AP Secretariat with 10-12 members.

The goals and key messages for health-care, decision makers and general public are given in **Table 1.** The goals were also numeric, e.g. allergy diets should drop 50% and asthma emergency visits 40% in 10 years. For each of the six AP goals, specific tasks, tools and evaluation methods were defined (6).

The messages of the AP were targeted to the whole population, to patients with allergy and asthma and their families, to public health and patient organisations, to experts, authorities and legislators.

The primary target groups of education and publicity were

health care professionals, authorities and persons responsible in day care centres, schools and other educational institutions,
key persons and peer workers in patient organisations, and media.

The AP messages were tested both among the professionals and patient population. In 2008 744 asthma contact persons (response rate 71%; 38% doctors, 62% nurses, 77% working in primary care) were surveyed by email ofthe programme goals and allergy management (9). The general messages were well received **(Table** Sl, in Supplementary Material). For example, GPs scored the message of *improving tolerance* 9.1 in a scale 4-10. The management processes and chains from GPs to specialists left, however, much to improve, e.g. doctors gave a low score of 5.4 to the availability and guidance for *specific immunotherapy.*

In 2011 allergic patients were employed in an internet-based gallup survey (10). The survey reached 1231 subjects and complete answers were obtained from 1094 subjects (response rate 89%, females 54%, mean age 45 years, range 15-89). The first message, *endorse health, not allergy* was ranked the most important by 54% of the responders while *avoidance of exposure as being the best approach* only by 13% **(Table** 82, in Supplementary Material).

Implementation

Finnish Lung Health Association (Filha, expert NGO, www.filha.fi), together with three other nongovernmental organizations Allergy & Asthma Federation, Finnish Lung Health Association, and Finnish Central Organization for Skin Patients were responsible for coordinating the implementation. Filha had the task to educate health-care professionals, and the other NGOs to implement AP to allergic subjects and general public. Due to the cooperation between NGOs, coordinated by a common project organisation (secretariat), implementation started in a relatively short time and targeted the whole population.

Contact person network

The educational action plan took advantage of the contact person network created already during the Asthma Programme 1994-2004 (11).

There are 21 hospital districts (5 university hospitals) in Finland. Primary health care services are provided by circa 250 primary care centres or units of municipal federations, including at least a 3-fold number of maternity and child health clinics and circa 1000 units of occupational health.

One-third of the last- mentioned units are private. In general, the private sector is responsible for a growing part of all health care services.

At baseline, in 2008, hospital based specialist clinics (paediatrics, pulmonary medicine), primary health care, part of the occupational sector, and pharmacies had circa 1 500 appointed asthma contact persons (doctors, nurses, pharmacists). For example, an asthma contact pharmacist was in 94% of the pharmacies in Finland. For the Asthma Programme this network of skilled contact persons was the key to effective implementation. The network weakened after the Asthma Programme, but was reactivated and strengthened as the contact persons continued their invaluable work further for the AP. The network has been completed by 157 nurses in maternity and child health clinics and in schools. Ten regional expert allergy groups in different parts of the country have started to coordinate local implementation and activities.

Education of health care professionals

Health care professionals are regionally educated by the hospital district, with the involvement of provincial governments. Filha coordinated this process with the help of two hired educators working together, a paediatrician and a nurse, who also attended almost all educational sessions performed in 2008-2013 covering the whole country. The local educators were mainly specialists in each hospital district (allergists, dermatologists, paediatricians, pulmonologists, rhinolaryngologists, and specialists in primary health care as well as nurses specifically trained in the area). Education took place in own locales of the health care during the normal office hours as part of the regular educational programmes.

The 21 hospital districts carried out a three-step educational process: 1) two hour AP launch sessions for opinion leaders, coordinators, and educators ofNGOs, 2) educational sessions in large health centres, 3) one day courses in central hospitals for local health care personnel. In years 2008-2013 Filha organized 204 educational events with around 12 000 participants (25 % physicians, 50% nurses, 10% pharmacists, 15% others). The main themes were: allergy-healthy child, anaphylaxis, food allergy, more tolerance -less allergy, and asthma **(Table** S3, in Supplementary Material).

The main educational material for professionals is listed in **Table** 2. As the key issue was to improve tolerance in practice, simple guidance was given **(Table** 3).

Patient education and public communication

Patient organisations arranged regional education to their key persons and peer workers and had a major impact in direct patient counseling and distributing free of charge booklets, videos (e.g. anaphylaxis), and CD-ROMS concerning asthma, allergy, smoking, indoor air quality, and ambient air pollution. This education was partly linked to the education of health care personnel. The Allergy and Asthma Federation and the Finnish Lung Health Association organised annually circa 10 public events in different parts of the country, and educated personnel in regional offices during the first five years of the AP. The AP secretariat produced material for guided self-management, and the patient organizations other material needed in Finnish and partly in Swedish **(Table 2).**

- publicity material for authorities, media and population
- education material to regional offices
- educational material for patients (self-management) and population (general information)

Education continued also to key persons in pharmacies, in day care centres and schools. Association of Finnish Pharmacies produced material and campaigns in allergic rhinitis and atopic eczema during 2009-2012. Association of Kindergarten Teachers in Finland planned a pilot campaign "Go to nature!" for 2014-15 in South-Karelia, incorporating various outdoors activities to the day care routine. If successful, new early childhood education guidelines will be introduced to whole country.

In 2011 the three NGOs started a joint campaign to increase allergy awareness and knowledge among patients and general public, by employing internet (website: allergyhealth.fi, social media, banner campaigns), radio (advertisements) and TV (news, talk shows). Nearly two million Finns were reached 2011-2013. Main focuses were allergy health (contacts to natural environments) and guided self-management.

Measuring outcomes

For outcome evaluation, the Finnish health care registers provided an invaluable data source. Especially, the hospital admission register ofNational Institute for Health & Welfare and drug reimbursement register of Social Insurance Institute of Finland (SII) were employed. The latter includes all patients in Finland with persistent asthma entitled to special cost reimbursement when purchasing asthma drugs. The asthma reimbursement code identifies patients with correctly diagnosed asthma with great accuracy, because the diagnosis is verified by objective lung function

measurements. For occupational diseases, Finland has a strict legislation and all verified cases are registered by the National Institute of Occupational Health.

For anaphylaxis, the Finnish anaphylaxis register was established in 2000 at the Skin and Allergy Hospital of the Helsinki University Central Hospital (12). Physicians (mostly allergists) from the whole country voluntarily report cases of severe allergic reactions independently of the causative agent. A one-page questionnaire form is available on the Internet.

Allergy and asthma costs in 2011 were thoroughly analysed using all possible data sources in collaboration with governmental officials. National Registry data were combined to evaluate all costs of allergy and asthma. These data included comprehensive direct health care costs including medications, hospitalizations, and visits to all health care providers.

Funding

Ministry of Welfare & Health allocated annually € 60-65 000 for the educational and coordinating work. The education of health care professionals was organized by the expert NGO, Filha, which also received some sponsorship from pharmaceutical companies. The latter did not influence the general principles of AP or the management strategies, e.g. self-management guidelines. The allergy control cards (rip-off sheets for patients) did not include any product names but a common statement: *AP in collaboration with the company in question.* The arrangement improved the dissemination of educational material to the doctors. For patient education and public communication the three other NGOs together received 2011-13 annually € 200 000 from Finland's Slot Machine Association (RAY). The main purpose of the governmentally regulated RAY is to raise funds through gaming operations to promote Finnish health and welfare. The education of health care professionals was costly, as was launching the messages among general public. After that, the implementation costs were minimal as the work was integrated to the regular work of doctors, nurses, pharmacists and administrators. The AP secretariat or public health personnel taking part of the activities did not receive any extra payment.

Results

Are we achieving the goals?

The interim, 5-year results of the 10-year Programme are given as answers to the six preset goals, and more specifically as response to the numerical indicators of achieving the goals.

1. To prevent development of allergy symptoms

Indicator: Prevalence of asthma, allergic rhinitis, atopic eczema and contact dermatitis is decreased by 20%.

In terms of disease prevalence and incidence, data is not yet available from follow-up studies. Long-term follow-up of young men (conscripts) is in process (13). Trends in prevalence of asthma and allergy are examined using repeated cross sectional surveys (FinEsS, The allergy, asthma and COPD study of Finland, Estonia and Sweden) (14, 15).

2. To increase tolerance against allergens

Indicator: Food allergy diets are decreased by 50%.

A formal study has been planned to survey and intervene the food allergy diets in day-care in Helsinki metropol area (nearly 1000 children in the intervention and control day-care centers). In 2012, a questionnaire was used to find out communal costs of diets in five cities (population close to 500 000). Allergy diets constituted approximately 6% of all meals in day care centres and 3-4% at elementary schools. On the national level, this means 6, 8 million meals restricted by allergy. In the city ofRauma (population 40 000), new recommendations for food allergy diets were implemented in day-care and schools. In 2011, 14% of children in Rauma had a special diet and in 2013 8% (N=5869 children 2013). The change was most marked in children from 7-12 years of age. In Espoo, the second largest city in Finland (population 259 000), the share of allergy diets in day-care centers were in 2012 only about 4% simply by starting to use recommendations given by AP. In comparison, the figure was still 7-8% in the neighbor community ofVantaa. Similarly, a 20-30% decrease in the number of allergy diets was achieved in a few years in the cities of Kotka and Lahti only by checking the true need of diets.

In 2008 allergen specific immunotherapy was received by 3675 patients (7/10 000) and it increased to 4909 patients in 2012 (+34%). The treatment is still at a low level in Finland compared to other Nordic countries (30/10000 in Norway).

3. To improve allergy diagnostics

Indicator: All patients are tested in quality certified allergy centres.

Fifteen allergy testing centres, including all 5 University Hospitals, have been audited for good diagnostic practice and 12 centres given a certificate for good diagnostic practice. These centres cover around 80% of the testing in public health. Lack of resources has restrained to expand the activity to the private sector, where testing practices vary most and revenue expectations dominate. However, two private sector testing units have received the certificate.

4. To reduce work-related allergies

Indicator: Occupational allergic diseases are decreased by 50%.

The number of verified cases of occupational asthma (accepted and compensated by insurance companies) decreased from 116 in 2007 to 57 in 2011 (-51%) **(Fig. 1).** The cases of allergic rhinitis decreased from 62 to 38 (-39%), respectively. Irritant contact dermatitis was the most prevalent occupational skin disease in 2007 with 222 verified cases decreasing to 144 in 2011 (-35%). Allergic contact dermatitis followed with 183 verified cases in 2007 and 114 in 2011 (-38%). The decrease is not explained by the changes in workforce (2 492 000 in 2007 and 2 470 000 in 2011).

5. To allocate resources to manage and prevent exacerbations of severe allergies

Indicator: Allergy control cards for guided self-management are in use in the whole country and asthma emergency visits are decreased by 40%.

Emergency visits caused by asthma have decreased in all age groups, and overall 42% in the 2000s **(Fig. 2).** In children (0-15 years) the improvement was most marked (-58%). Asthma seems to become a milder disease, or better controlled, according to a pharmacy barometer survey. Ten per cent of 3062 asthmatics (mean age 49 years) evaluated their disease as severe in 2001 vs. 4% of 1114 asthmatics (mean age 51 years) in 2010 (15). In the comparison of2001 and 2010 cohorts, emergency visits during the previous year had dropped from 34% to 14% and hospitalizations from 18% to 6%.

Although the number of asthmatics on maintenance treatment, ie. patients entitled to special reimbursement for their drug costs, has increased 27% in the 2000s, hospital days have been in steady decline (-62 %) **(Fig. 2).** To reduce them further needs risk group thinking as elderly women, 60 years or older, should be in focus (16). The number of new patients to the special asthma reimbursement register is in slight decline **(Fig. 2).**

Anaphylaxis emergency visits have doubled in 12 years (277 cases in 2000 and 585 in 2012), and increased especially in children (53 vs.l53 cases). The anaphylaxis emergencies differ between regions probably telling more of the variable health care practices than of true differences in morbidity (17). The anaphylaxis register received 1036 voluntary reports of anaphylaxis 2000-2012 (42% children, 60% of all had received epinephrine). They represent only a small part of all the cases in Finland. The distribution of causative agents differed markedly in children (72% foods, 10% drugs) compared to adults (41% foods, 37% drugs) (Fig. 3).

Asthma mortality has been very low, in 2006-11 on average 8 annual deaths (range 4-12) under the age of 60 years (Fig. 4). Twenty-three people have died in anaphylaxis during the last 14 years (1998-20 11): 14 bee or wasp stings, 4 foods (1 peanut), 3 drugs, 1 snake bite, 1 unknown.

6. To decrease costs due to allergic diseases
Indicator: Predefined all allergy costs are reduced by 20%.

In 2011 direct allergy costs (drugs, hospital days, out-patient visits, rehabilitation, allergy diets in schools) were € 314 million, including asthma (18). Asthma caused 65% ofthe direct costs and drugs half of the costs. Together direct and indirect costs (days off-work, disability pensions, productivity loss) were € 1, 3-1, 6 billion, i.e. indirect costs were 3-4 fold higher than direct costs. The distribution of the costs by allergic condition is given in Fig. 5, and the development of allergy costs 2000-11 in Fig. 6. Direct allergy costs and costs of disability pensions decreased 9% during the first decade of 2000s.

Marked asthma cost-savings took place 1993-2003 during the Asthma Programme (11). In 2007, a year before start of AP, direct asthma costs and costs of disability pensions were around € 250 million and € 227 million (-9%) in 2011.

Smoking

As one of the messages was *stop smoking,* the trends were followed. During the period 2004-07 overall27% of Finnish men smoked, in 2008-2011 23%. For women the figures were 19 % and 16%, respectively. Smoking has markedly decreased in the population of higher education: in 2008-2011 13% of men and 9% of women smoked. Smoking did not decrease in less educated population, and even increased in women. The most remarkable change for better was observed in occupational exposure among restaurant workers as the share of non-exposed workers climbed

up from around 30% to 80% during the period of 1999-2009 (19). This was a result of legislation. Restaurants had to be smoke free in 2009.

Discussion

Several health care indicators in Finland show that allergy burden is levelling off and even decreasing. Asthma emergency visits and need for hospital treatment have dropped steadily in the whole country, although anaphylaxis have caused even increased visits. This is probably a result of the anaphylaxis awareness campaign and education launched by the AP, but we cannot exclude true morbidity change. Allergy diets in children and occupational allergies are in rapid decline. Asthma is better controlled and less severe, which logically is reflected in shrinking costs. The single most important cost driver of direct costs was medication, as observed also in other studies (20). Direct allergy costs have reduced 9%. For comparison, the direct costs of diabetes in Finland rose 60% in 2000-2007 and costs of disability pensions 50% (21).

Studies before kick-off of the AP in 2008 indicated that asthma and rhinitis are still on rise. Finnish National Population Registry based random postal survey in adults resulted in prevalence of6, 5% ofphysician-diagnosed asthma in 1996 and 10% in 2006 (22). For rhinoconjunctivitis the respective figures were 37, 2% and 44, 4%. In the city of Helsinki, same kind of random postal survey in adults, 20-69 years, showed increase for asthma from 6, 8% (1996) to 9, 4% (2007) and for rhinoconjunctivitis from 38, 0 to 40, 9 (23). At the moment it is too early to evaluate the development of allergy incidence, but data from Canada and non-English speaking countries in Europe have shown already for some time that the peak in asthma prevalence might have been reached at the level of 8-12% (24).

The Finnish initiative was a comprehensive and multidisciplinary plan, based on new knowledge, to change the course of allergy in the society. The action programme was not only including strategies for prevention and treatment, but also an operational plan for their dissemination and implementation. Production of guidelines is meaningless if they are not used in practice. Effective implementation strategies use multiple methods, decision support system, and interactive education. State administrators, patient organizations, nurses, pharmacists and importantly GPs took part in the planning of the AP. They were also the keys to the successful networking and contacts with local health centers, maternity clinics, day-care centers and

schools. They were also instrumental in creating regional and local treatment improvements. In practice, implementation acted through this network of local GPs, nurses, pharmacists, i.e. public health coordinators. Much work was, however, needed to create new motivation at the start of AP. Health-care organizations are complex, conservative and suspicious to make major changes **(Table** 7). The idea of taking steps from treatment to prevention was, nevertheless, highly acceptable in the Finnish society, and the steps from passive "wait and see" attitude to more active approach to treatment and severe allergies were praised by the professionals.

Allergy management in change

At the patient level, the main tasks were straight forward. Strengthen both immunological and psychological tolerance and change attitudes to support health, not allergy (see **Table Sl).** Treat severe allergies early and effectively. Stop attacks and exacerbations proactively with guided self-management.

Mild allergic symptoms are common in children and young people and should not be medicalised unnecessarily. Mild allergy does not usually become more severe along time. The outcome is generally favorable (25). Lindstrom and coworkers (26) used the Finnish military register to follow 393 asthmatic young men for 20 years. At the age of 40, 52% of them were free of symptoms or had them only occasionally, 20% had mild persistent, 17% moderate persistent, 10% severe persistent asthma, and 80% had co-morbid allergic rhinitis.

Severe forms of allergy were in special focus as they cause most of the burden for individuals and society. To help patients proactively to stop exacerbations of severe allergies, allergy control cards for guided self-management were launched for major allergic conditions. Disease control was strongly emphasized as patients have been guided for self-management.

Early treatment of allergic inflammation was stressed (hitting early and hitting hard), and also in other conditions than asthma, like in atopic dermatitis (27). Importance of patient follow-up and long-term maintenance therapy was underlined. For children with mild persistent asthma (the majority!), a strategy of intermittent (periodic) treatment was developed (28). Immunotherapy and especially sublingual immunotherapy (SLIT) were advocated where feasible.

Food allergy diets were critically re-evaluated and stopped if possible. The AP was able to generate a true effort in the best interest of children to critically evaluate unwarranted allergy

diets, often based on old concepts and beliefs of allergenic foods. Day-care centres and schools were advised to abandon long lists, where parents can mark all possible foods suspected to give adverse reactions to their children. Better diagnostic work to indicate true and clinically significant food allergies was called for. Allergen component IgE diagnostics was taken into clinical practice and advocated in selected cases like peanut allergy. Avoidance must be based on proper evidence and be precise: what is avoided and how long? For severe cases, specific oral tolerance induction (SOTI) for milk, wheat and peanut was studied and increasingly employed in clinical practice (29, 30). Altogether, in patients with troublesome food allergies, a clear shift from passive avoidance to active treatment was taken.

The role of pro- and prebiotics in allergy prevention has been intensively studied, also in Finland (31). High-risk mothers and infants (N=1018) participated in a 5-year follow-up study of perinatal administration of a probiotic mixture or placebo (32). Probiotic bacteria conferred some protection against IgE-associated eczema at 2 years, but at 5 years the effect was only seen in the cesarean-delivered children. At the moment, the role of probiotics has not been established in the prevention or treatment of allergy (33).

Barriers in allergy care

A systematic approach to allergy is complicated by the heterogeneity of clinical manifestations and diseases. Allergic patients are taken care of many medical specialities and increasingly by GPs. In medical schools, allergy education is quite variable although the European Union Medical Specialists (UEMS) has put up some common standards. However, the status of allergology as a medical speciality varies from one country to another: full speciality, sub-speciality or not more than educational courses (34).

Study limitations

The whole Finnish population was the target, and no inclusion or exclusion criteria were employed. A "real-life" intervention without a proper control setting leaves room for scientific arguments, although a "real-life" approach gives a less selected and distorted outcomes (35). What would have happened without the AP? This is an argument large scale community actions face, and we do not know the answer. At least, AP coordinated and facilitated the existing efforts towards common goals and set a follow-up for critical assessment of any change. To evaluate the usefulness of AP, the questions of efficacy, effectiveness and cost effectiveness can be made. It seems obvious that AP did more good than harm, i.e. efficacy was acceptable. It worked in

practice and was enthusiastically received by health care professionals as well as majority of patients, i.e. effectiveness was proven. It reduced costs much more than was the expense of AP, i.e. AP was cost effective and worth to do.

International collaboration

The Finnish Programme, or parts of it, is associated with the World Allergy Organization (WAO) (1) and Global Alliance of Chronic Respiratory Diseases (WHO/GARD), a voluntary organization working for improving global lung health (36). The Programme is developed further and enlarged along with the European Commission Seventh Framework research project Mechanisms of Development of Allergy (MeDALL) (37). The Programme has also benefited from the co-operation with the European Allergy Network (GA2LEN), and the essential global guidelines and action plans, such as the Global Initiative for Asthma (GINA) (38, 39), as well as the Allergic Rhinitis and its Impact on Asthma (ARIA). A Norwegian Allergy Programme is under construction, and with the Finnish one, will give a model for others to modify and improve to meet their special needs. A smaller scale Programme is taken place in Korea, where multi-sector cooperation between government, academic institutions, private organizations, local communities, and media tackles allergy burden (40).

Asthma projects and programs in Argentina, Australia, Brazil, China, Japan, Mexico, Philippines, Russia, South-Africa and Turkey were discussed by a group of experts in asthma care (the Advancing Asthma Care Network, 41). The group concluded that the major barriers for successful programs are: 1) low rates of dissemination and implementation of treatment guidelines, 2) low levels of continuing medical education and training of primary health care professionals, and 3) poor access and distribution ofiCS. In the less developed asthma programs, under-recognition and under-treatment further limit the success.

Conclusion

It is the Finnish consensus, that allergy paradigm needs re-evaluation. New kinds of actions are needed, when allergic individuals are becoming a majority of Western populations and their numbers are increasing worldwide **(1,** 42). The costs are mounting and the recent estimate of annual costs of€ 1, 3-1, 6 billion in the Finnish population of 5, 4 million is alarming. With national and local action plans the challenge can be met. Allergy is a community problem needing community actions, which do work even though the local conditions and infrastructures

largely differ (43). The case Finland indicates that increase of allergy prevalence and costs is not inevitable. Major improvements can be achieved with relatively simple means, if the society is committed to reduce disease burden **(Fig.** S3). The international dimension of AP may help others to create better models, while learning from the successes and failures of the Finnish initiative. Preventing the increase in allergies and asthma will be a particularly important in areas with rapidly developing economy (1).

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Table 1. Allergy Programme goals and messages (6).

Goals for health-care

1. To prevent development of allergy symptoms:
Indicator: Prevalence of asthma, allergic rhinitis, atopic eczema and contact dermatitis is decreased by 20%.
2. To increase tolerance against allergens:
Indicator: Food allergy diets are decreased by 50%.
3. To improve allergy diagnostics:
Indicator: All patients are tested in quality certified allergy centres.
4. To reduce work-related allergies:
Indicator: Occupational allergic diseases are decreased by 50%.
5. To allocate resources to manage and prevent exacerbations of severe allergies:
Indicator: Allergy Control Cards for guided self-management are in use in the whole country and asthma emergency visits are decreased by 40%.
6. To decrease costs due to allergic diseases:
Indicator: Predefined all allergy costs are reduced by 20%.

Key messages for all

- Endorse health, not allergy
- Strengthen tolerance
- Adopt a new attitude to allergy. Avoid allergens only if mandatory.
- Recognise and treat severe allergies early. Prevent exacerbations.
- Improve indoor air quality. Stop smoking.

Table 2. Examples of the tools for practical implementation of the Allergy Programme. Disease or treatment specific guidelines are evidence-based.

Material for health-care professionals • atopic eczema guidelines, update 2009 • allergen specific immunotherapy guidelines, update 2012 • food allergy guidelines, update 2012 • asthma guidelines, update 2013 • allergy control, pocket guide 2011 • skin prick testing quality, pocket guide 2011 • allergy in children, practical recommendations 2011 • laboratory diagnostics in atopy (allergen components), pocket guide 2013
Guided self-management material for patients to stop exacerbations • asthma 2010 • allergic rhinitis 2010 • anaphylaxis 2010 • small children asthma 2011 • atopic eczema 2013
Additional material produced by the patient organizations (NGOs)

Table 3. Practical advice to build-up and improve tolerance as well as prevent symptoms and exacerbations/attacks (5).

Primary prevention

- Support breastfeeding, solid foods from 4-6 months
- Do not avoid environmental exposure unnecessarily (e.g. foods, pets)
- Strengthen immunity by increasing connection to natural environments
- Strengthen immunity by regular physical exercise
- Strengthen immunity by healthy diet, e.g. traditional Mediterranean or Baltic type
- Use antibiotics only for true need, majority of microbes are useful and build healthy immune function
- Probiotic bacteria in fermented food or other preparations may strengthen immune function
- Do not smoke, e.g. parents smoking increase asthma risk in children

Secondary and tertiary prevention

- Regular physical exercise is anti-inflammatory
- Healthy diet is anti-inflammatory, e.g. traditional Mediterranean or Baltic type of diet improves asthma control
- Probiotic bacteria in fermented food or other preparations may be anti-inflammatory
- Allergen specific immunotherapy:
  -allergens as is (foods)
  - sublingual tablets or drops (SLIT) (pollens, mites)
  -subcutaneous injections (e.g. insect stings)
- Hit early and hit hard respiratory/skin inflammation with medication. Find maintenance treatment for long-term control
- Do not smoke, asthma and allergy drugs do not have full effects in smokers

Figure 1. Verified occupational respiratory and dermatological allergies in 2007-2011 (14).

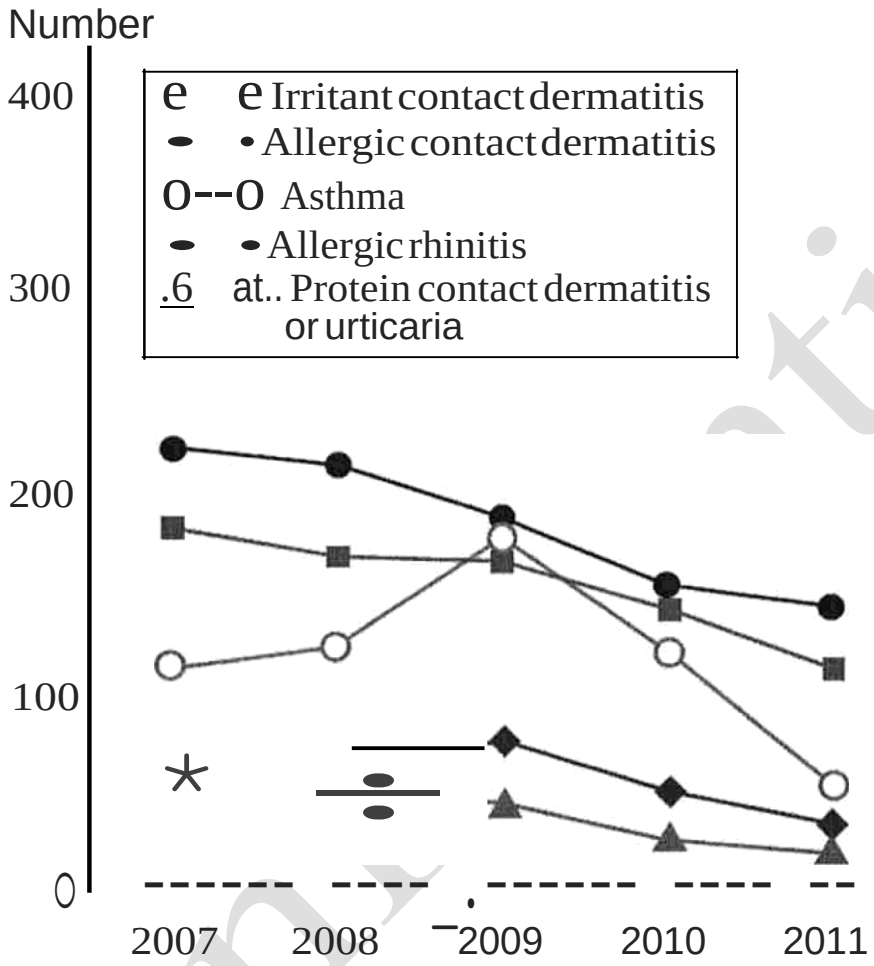


Figure 2. Observation period for asthma 2000-2012. Numbers are relative changes after 2000 (index=O). (A) Changes in asthma emergency visits by age groups. (B) Increase in the number of asthma patients entitled to special reimbursement for their drug costs (persistent disease), number of new patients entitled to special reimbursement, and decrease in hospital days (in 2012 12343 days, 2622 patients, average stay 3, 9 days).

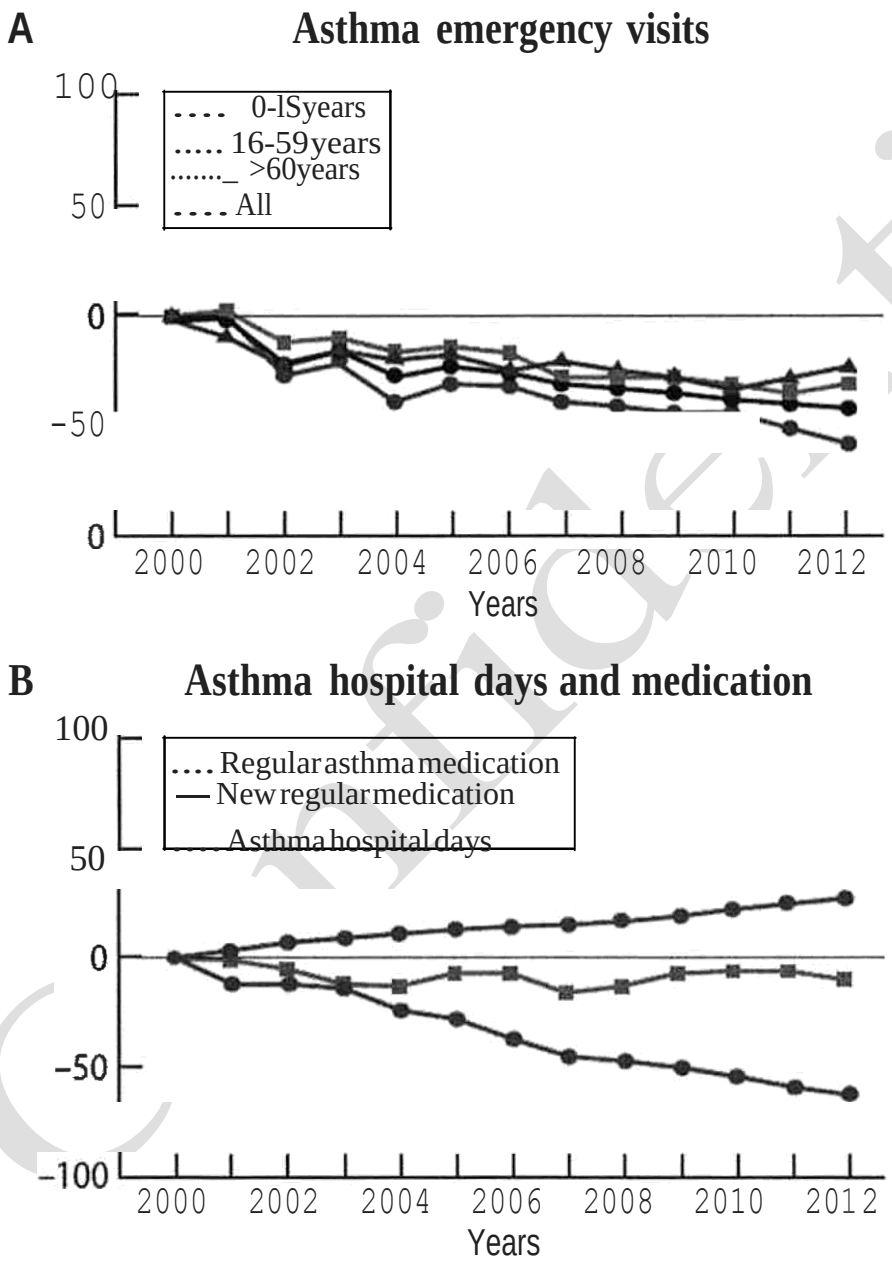


Figure 3. Causes for severe allergic reactions, anaphylaxis(%) in children and adults 2000-2012 (N=1036, 42% children). Makinen-Kiljunen S. The Finnish Anaphylaxis Register 2013.

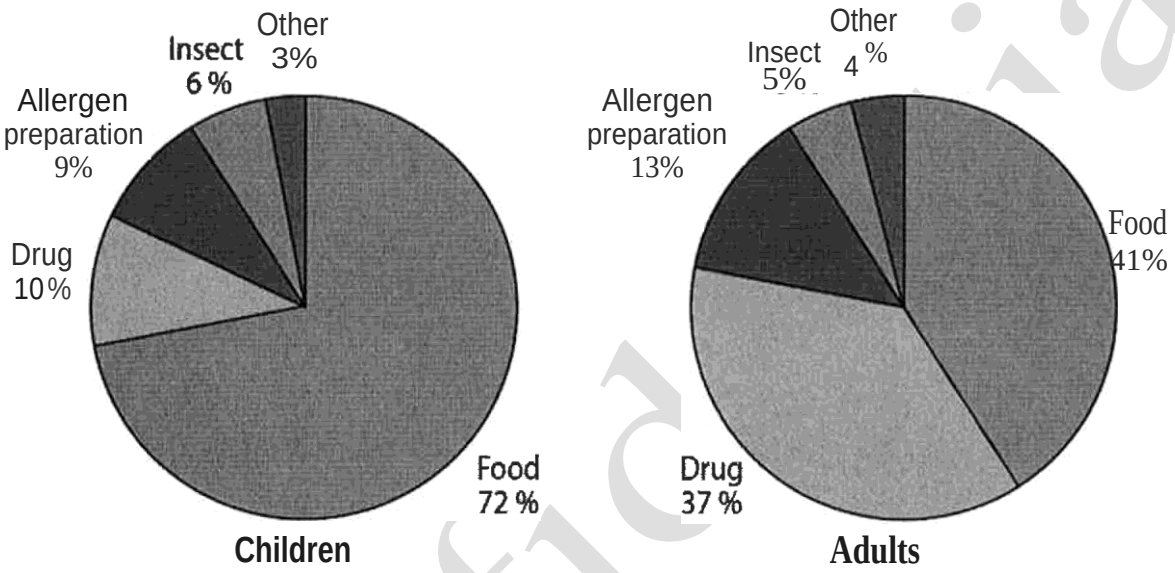


Figure 4. Astluna mortality under the age of 60 years 1971-2011. Official Statistics of Finland: Causes of death (e-pub.).

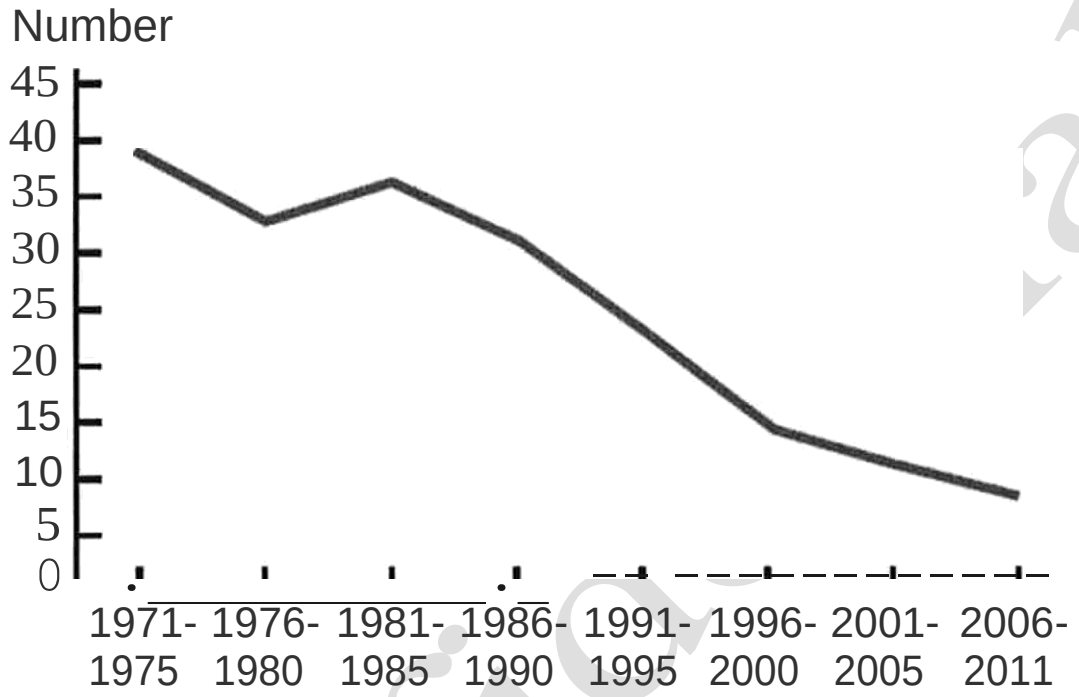


Figure 5. Distribution of direct health care costs by the most important allergic conditions in Finland 2011 (18). Total direct costs € 314 million (asthma costs 65%).

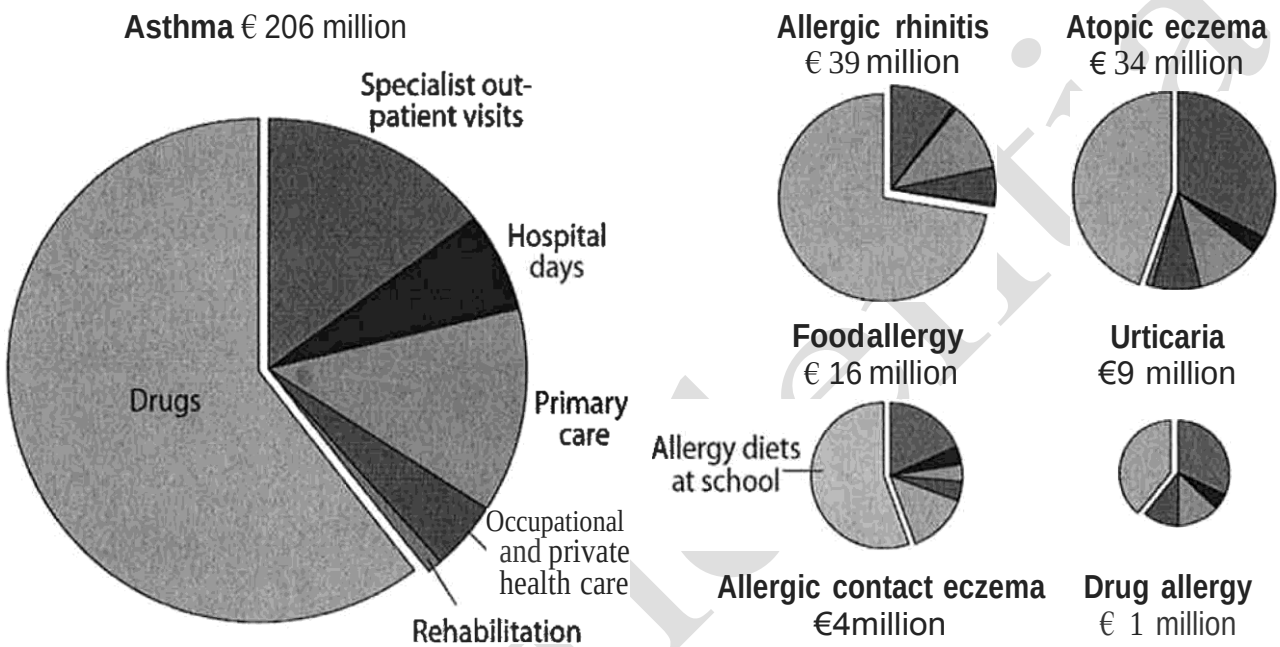


Figure 6. Change of asthma and allergy costs in Finland (population 5, 4 million). (A) Change of drug costs, specialist care, rehabilitation and disability pensions. Numbers are relative changes after 2000 (index= 0). (B) Changes in the drug costs by drug category 1995 2011. Total sales of all drugs in the country on the right.

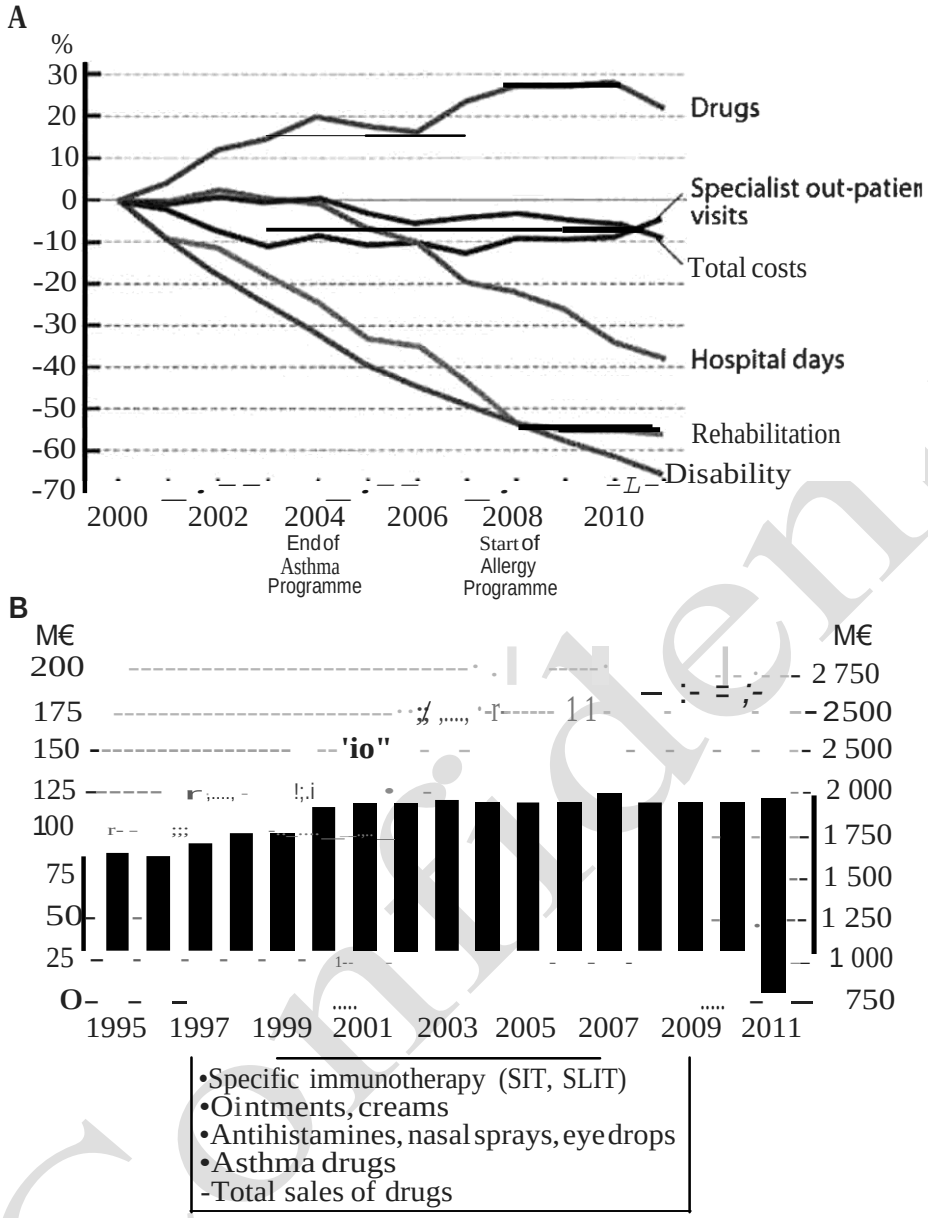


Figure 7. Action for implementation and barriers to progress.

New action

- Introducing new knowledge (lack of tolerance, biodiversity hypothesis)
- Renewing motivation, changing attitudes
- Employing unused know-how
- Organizing resources to common goals
- Activating interest groups and stakeholders to participate

Barriers to progress

- Turning knowledge and goals into practice is conditioned by individuals and organizations
- Real-life practice already deals with complexity of issues and variety of values
- Real-life take-up of new knowledge is constrained by rigidity and path dependence
- Excuses and true reasons not to act: lack of money, personnel, facilities, time
- Need to be constructive and take an adaptive and collaborative approach to implementation

Supplementary Tables Sl-S3

Table Sl. Evaluation of Allergy Programme key messages and allergy management in 2008, at the beginning of the progranune, by asthma contact doctors and nurses working mainly in primary care. Score 4-10 (9).

Programme messages	Nurses	Doctors
• endorse health, not allergy	8,8	9,2
• strengthen tolerance	8,7	9,1
• adopt a new attitude to allergy	8,7	9,3
• avoid allergens only if mandatory		
• treat severe allergies early	9,2	9,5
• Improve air quality. Stop smoking	9,6	9,6
Treatment processes (GP- specialist co-operation)		
• asthma	7,8	6,6
• asthma in children	7,7	6,8
• food allergy	7,2	5,9
• specific immunotherapy	7,6	5,4
• need for allergy training	9,1	9,0

Table S2. Allergic patients were asked for awareness of the Allergy Programme in 2011. They were told the Programme's key messages and asked for preferences (N=1094, mean age 45 years) (10).

Are you aware of the National Allergy Programme?	
• have not heard about it	77%
• heard people to discuss of it	13%
• noted in newspapers, TV or radio	5%
• noted in internet or elsewhere	1%
• no opinion	4%
What are the most appropriate messages of the Allergy Programme?	
• endorse health, not allergy	54 %
• stop smoking	46%
• do not avoid allergens unnecessarily	39%
• take it easy with allergy	35%
• contact with nature supports health in allergic patients	26%
• drugs are enough to control allergy	15%
• avoidance of exposure is the best approach	13%
• improving hygiene is the best approach	11%
• none of the above or some other aim	4%
•oo nioo	

Table S3. Educational process for health care professionals 2008-2013.

Themes	2008	2009	2010	2011	2012	2013	**Total**
Programme launch • central hospitals	16	10					26 events 1585 participants
Food allergy • primary care	7	29	25	8	1		70 2353 participants
Allergy health • central hosp districts		3	10	11			24 events 2293 participants
Anaphylaxis • primary care			1	16	15	16	48 events 3232
Allergy-healthy child • central hosp districts					8	6	14 events 912 participants
More tolerance -less allergy • central hosp districts					10	4	14 events 1031 participants
Asthma • central hosp districts						1	1 event 83 participants
• Lapland • Military Forces etc.			1	1	5		7 events 442 participants
All15.10.2013	23	42	37	36	39	27	204 11931 participants

Supplementary Figures Sl-S3

Figure Sl. The early steps of the Finnish Allergy Programme 2008-2018.

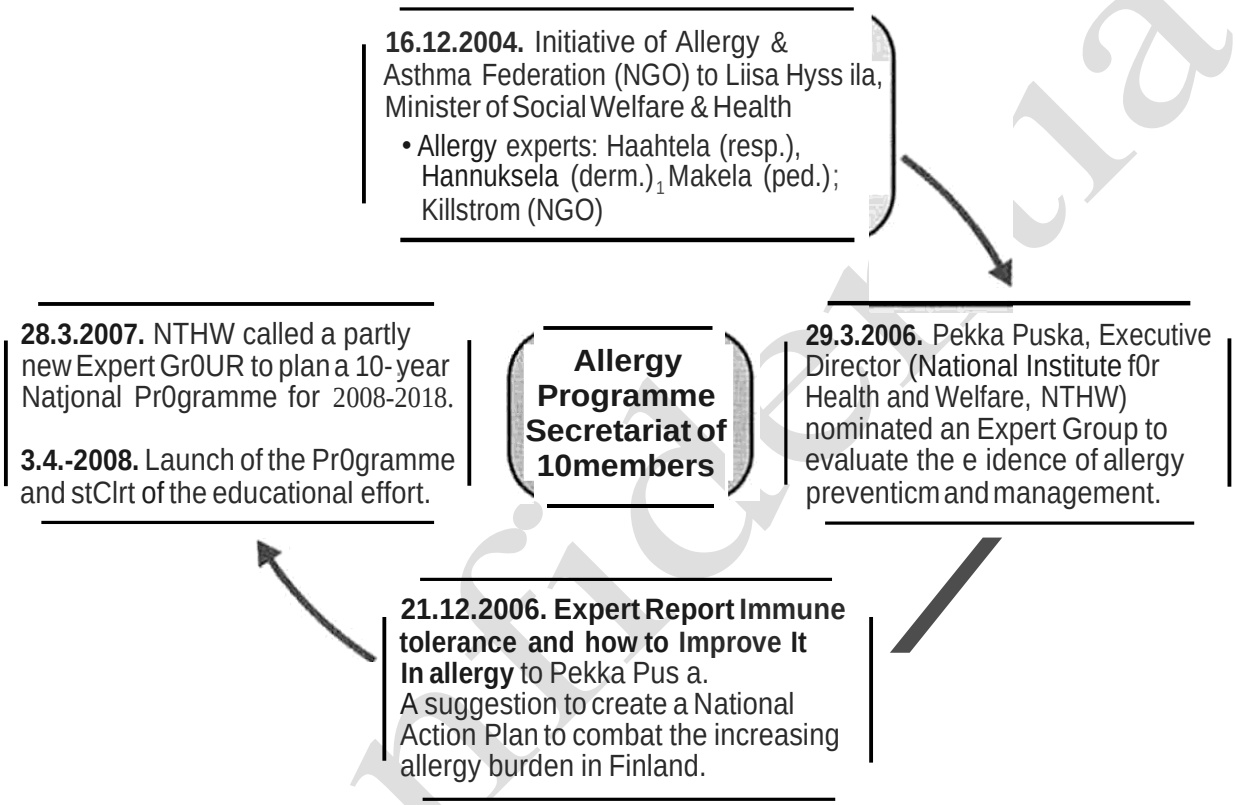


Figure S2. Organisational structure for implementation.

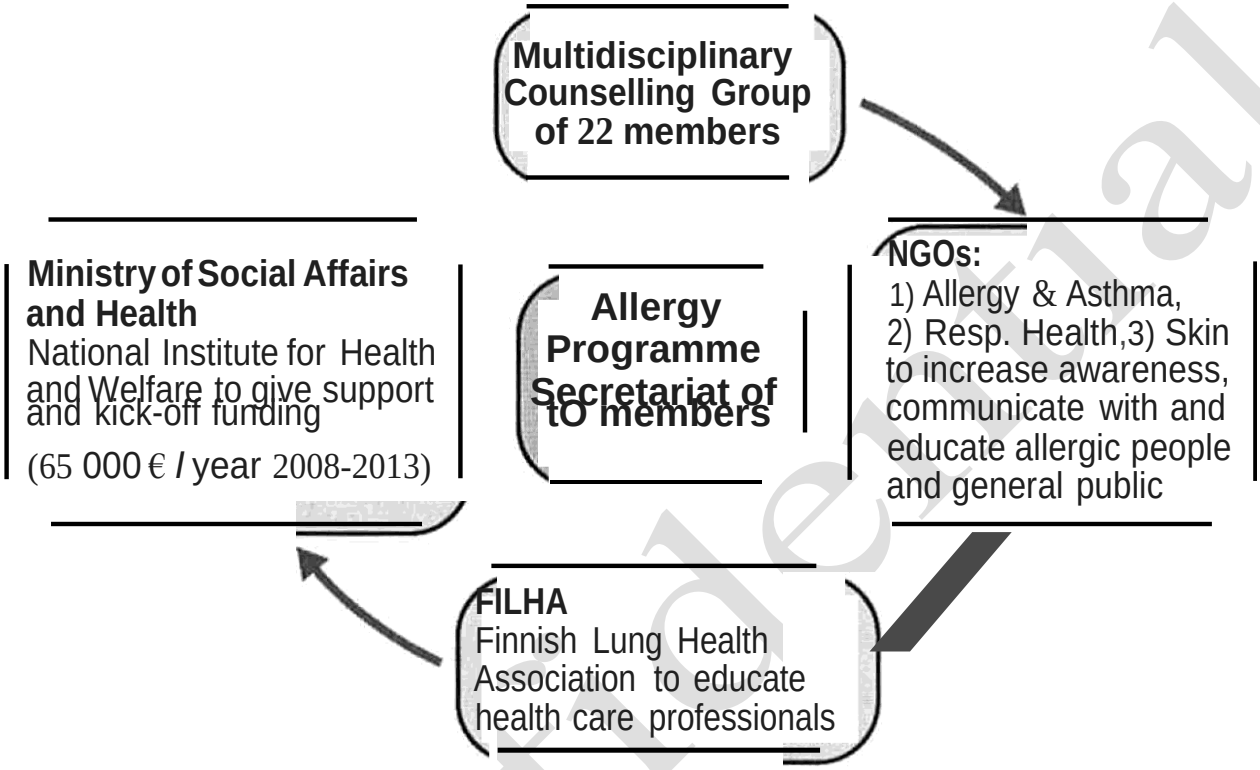
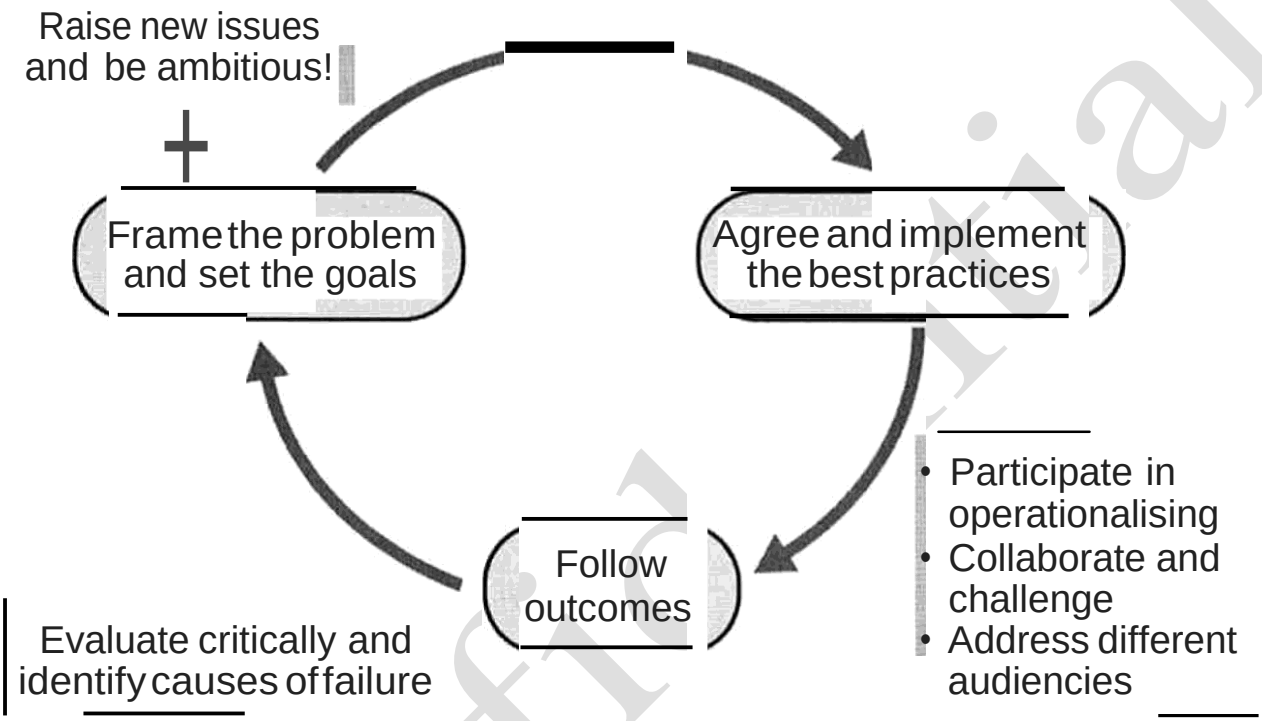


Figure S3. From research to guidelines and best practices.



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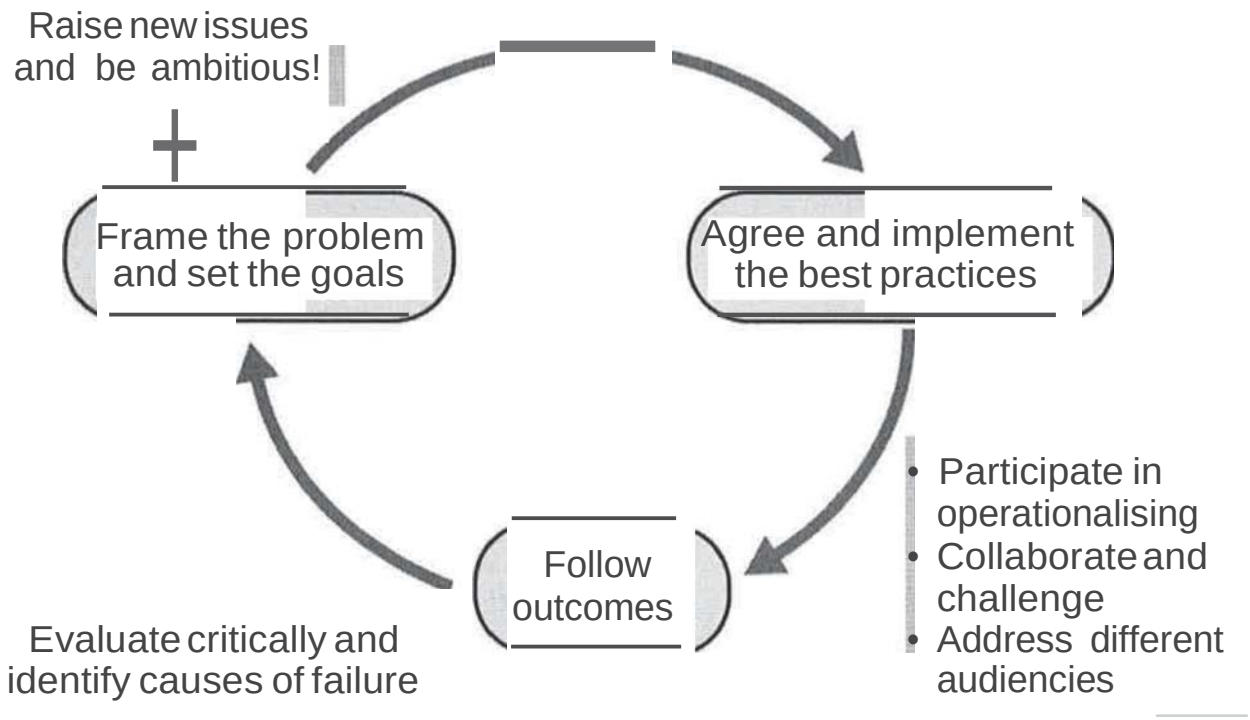

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The significance of early recurrent wheeze for asthma outcomes in late childhood

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ABSTRACT: Recurrent early life wheeze is not always asthma, and up to 50% of children are reported to remit. With reports of adult asthma symptom relapse, we assessed the prognosis of recurrent bronchial obstruction (rBO) through adolescence in the Environment and Childhood Asthma (ECA) prospective birth cohort study.

The present study is based on data from investigations at ages 2, 10 and 16 years of 550 young people (52% males) attending at 16 years of age. Based on the presence of rBO from 0–2 years, defined as recurrent (at least two episodes) doctor-diagnosed wheeze, and asthma from 2–10 years and 10–16 years, defined as at least two episodes of doctor-diagnosed asthma, symptoms and medication use, prognosis of rBO was assessed. Bronchial hyperresponsiveness (BHR) was diagnosed by a metacholine provocation dose f8 mmol that caused 20% reduction in the forced expiratory volume in 1 s.

At 10–16 years, 34% of the 143 rBO children had asthma. All children with rBO had reduced lung function compared with the never asthmatics. Of the rBO children in remission, 48.4% had asthma symptoms, medication use and/or BHR compared with 26.7% with never asthma (p,0.001).

Only 34.3% of rBO children were without asthma symptoms, medication use or BHR by 16 years, possibly indicating future asthma risk.

KEYWORDS: Adolescence, bronchial hyperreactivity, paediatric asthma, wheeze

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Wheezing in the first few years of life is a common [1] but complex condition with several causes and outcomes [2]. The long-term prognosis and variable presentation of asthma-like symptoms is highlighted in many prospective studies from birth to school age [3–5], and from childhood into adulthood [2, 6–10]. The observed natural course of wheeze in the first years of life varies, with reports of up to 50–70% of children ''out-growing'' their symptoms during school age [9, 11, 12].

However, early childhood respiratory disease increases the risk of adult asthma [13, 14] and chronic obstructive pulmonary disease (COPD) [15, 16]. Most cases of asthma start in the first few years of life [17], and the clinical presentation of asthma varies by a remitting and relapsing pattern [18, 19]. It is not clear at what age (if any) it can be said that asthma (-like) symptoms are ''outgrown'', as it is possible that benign wheeze is a different condition to early asthma presentation. Although wheeze is a hallmark of asthma, it may represent other disease entities. Thus, using wheeze as a proxy for asthma is insufficient for understanding disease prevalence and progression [20]. Other surrogate measures of asthma, such as reduced lung function and bronchial hyperresponsiveness (BHR) are important characteristics of asthma that support, but do not define, asthma.

Based on the heterogeneity of asthma in childhood, some authors suggest that asthma should not be used to describe wheezing illness in preschool children [21]. However, failing to do so might impair or delay appropriate treatment and management, and is clearly erroneous for many children. To date, we are largely unable to identify those with benign wheeze (not to recur later in childhood or adulthood) from those with an early asthma debut.

In the Environment and Childhood Asthma (ECA) prospective birth cohort study in Oslo, Norway, we aimed to assess the prognosis through adolescence of recurrent bronchial obstruction in early life, focusing on disease remission and recurrence.

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SUBJECTS AND METHODS

Study design

The present study includes data from the 0–2-, 2–10- and 10–16-year intervals obtained at the 2-, 10- and 16-year follow-up investigations that were part of the ECA study in Oslo. This population-based prospective birth-cohort study included 3754 healthy newborns born during 1 year (1992–1993), of whom 802 had lung function at birth measured by tidal breathing flow–volume loops (time to peak expiratory flow/total expiratory time) [22]. Follow-up investigations were performed at 2 years (a nested case–control study of 516 out of 612 identified children with recurrent physician-diagnosed wheeze and healthy controls), 10 years (1019 out of 1215 invited children who had lung function measured at birth or included in the 2-year case–control study) and at 16 years of age (550 of the same 1215 children) (fig. 1).

0–2 years

Questionnaires at birth, and at 6, 12, 18, and 24 months, included detailed family and personal history of allergic diseases, health-related factors, and socioeconomic and environmental factors [1].

Registration cards documenting the presence of the following respiratory symptoms were completed at any doctor contact: tachypnoea, wheezing, expiratory stridor, respiratory chest retractions and sibilations/whistles. If o3 respiratory symptoms were documented o2 times, or if such an episode lasted o4 weeks, the subject was classified as suffering from recurrent bronchial obstruction (rBO).

At 2 years of age

The study paediatrician conducted a parental interview and clinical investigation including measuring tidal flow–volume loops before and after inhaled nebulised salbutamol [23, 24].

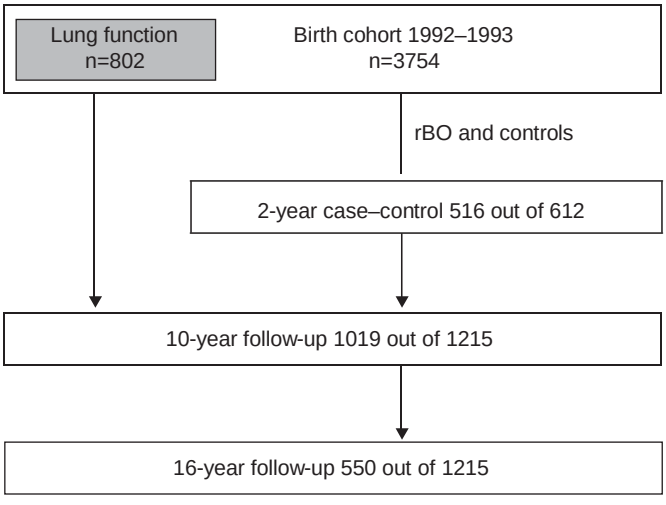

FIGURE 1. Flow chart of the children included in the Environment and Childhood Asthma study in Oslo, Norway. The overall attendance rate at the 10-year follow-up was 84%, while it was 45% at the 16-year follow-up. rBO: recurrent bronchial obstruction.

At 10 years of age

A clinical investigation included parental interview, skin prick test (SPT) for allergic sensitisation, forced expiratory flow–volume loops for lung function measures, and metacholine challenge test for BHR [1].

At 16 years of age

A clinical investigation included an interview with the subject, SPT, lung function measurements and a metacholine challenge.

All investigations required at least 4 weeks without symptoms of respiratory tract infection, no use of antihistamines for 120 h, leukotriene antagonists for 72 h, short- or long-acting b_2 agonists for 12 or 48 h or inhaled corticosteroids (ICS) for 12 h.

Written informed consent forms were obtained from parents at all phases, as well as from the subjects at 16 years of age. The study was approved by the Regional Medical Ethics Committee (Oslo, Norway) and the Norwegian Data Inspectorate and reported to the Norwegian Biobank Registry (Oslo, Norway).

Subjects and representability

The present study comprises all 550 subjects (52% males) attending the 16-year follow-up study, giving an attendance rate of 53% of the 10-year participants. The included study population was largely comparable to the entire cohort at birth, with a few exceptions. Study participants more often had older siblings, the family income was higher, and parental rhinitis was reported with borderline significance, whereas the subjects were similar in terms of parental atopic dermatitis, asthma, smoking habits and pet keeping (table 1).

In the entire cohort, 306 children were identified with rBO giving a prevalence of 8.3%. The children with rBO included in the nested case–control study at 2 years had significantly lower tidal lung function and a greater bronchodilator response than the healthy controls, as previously reported [23].

The children attending both the 10- and 16-year investigations were, at 10 years, slightly younger, slightly shorter, weighed less and were less often sensitised to at least one allergen than those who did not attend the 16-year investigation. However, they were similar in terms of personal or parental asthma, allergic rhinitis, atopic dermatitis and measured lung function (see table S1).

Methods

Questions used at each time-point for the questionnaires, interviews and reported information are given in table S2.

At 10 and 16 years

The physician conducted parental and study subject interview (at 10 and 16 years, respectively) focused on the child's symptoms of asthma and other allergic disease and their respective management during the last 12 months, as well as in the period since the previous investigation.

Investigations at 16 years

Clinical investigations were performed by experienced paediatricians at every follow-up visit.

TABLE 1 Demography at birth for the subjects completing the 16-year follow-up compared with the remainder of the birth cohort (total included at birth n53754)

	Included at 16 years	Not included at 16 years	p-value included versus not included
Subjects n	550	3204	
Males	285 (51.8)	1658 (51.7)	0.98
Parental asthma	69 (12.5)	387 (12.1)	0.78
Parental rhinoconjunctivitis	171 (31.1)	865 (27.0)	0.050
Parental atopic eczema	164 (29.8)	906 (28.3)	0.47
Maternal smoking during pregnancy	133 (24.2)	782 (24.4)	0.89
Number of siblings	0.6¡0.7	0.5¡0.7	0.009
Having older siblings	269 (50.9)[#]	1334 (43.8)[¨]	0.003
Dog in the house	44 (8.0)	300 (9.4)	0.34
Cat in the house	39 (7.1)	243 (7.6)	0.73
Paternal permanent employment	502 (93.1)[+]	2877 (92)[1]	0.37
Family gross income category	3.9¡0.9	3.7¡1.0	0.007
Maternal year of birth	1962 (1947–1972)	1962 (1946–1972)	
Paternal year of birth	1960 (1937–1971)	1960(1935–1976)	
Maternal education category	4.5¡1.2	4.4¡1.3	0.10
Paternal education category	4.6¡1.3	4.6¡1.4	0.94
Years parents have lived together	5.4¡3.4	5.3¡3.6	0.35
Parents living together	522 (95.3)[e]	2995 (93.8)[##]	0.18
rBO at 2 years	143 (26.0)[¨¨]	159 (5.1)[++]	,0.001

Data are presented as n (%), mean¡SD or median (minimum–maximum), unless otherwise stated. 1250 subjects were invited for follow-up at 10 and 16 years (those with lung function measured at birth and/or who participated in the nested case–control study of recurrent bronchial obstruction (rBO) at 2 years). Parental disease is reported as the presence of disease in at least one of the parents. Family income is given in five categories: from 1 (,100 000 NOK) to 5 (.500 000 NOK). Parental education is given in six categories from 1 (maximum 9 years at elementary school) to 6 (university degree). [#]: n5529; [¨]: n53044; [+]: n5539; [1]:n53126; [e]: n5548; [##]: n5319; [¨¨]: n5550; [++]: n53117.

SPTs, performed according to European standards, tested for common inhalant and food allergens, which included house dust mites, pets, grass, tree and mugwort pollens and moulds, as well as cow's milk, wheat, peanut and cod, using allergens from Alyostal[1] (Stallergenes, Antony, France), ALK prick SQ (ALK Scherax, Wedel, Germany) and Allergopharma[1] (Hørsholm, Denmark) (see online supplementary material for details).

Lung function (at 10 and 16 years of age) was measured by maximally forced expiratory lung function loops with a Sensormedics V-max (Sensormedics Diagnostics, Yorba Linda, CA, USA) spirometer. The results are reported as % predicted (% pred) values of forced expiratory volume in 1 s (FEV_1) and forced expiratory flow at 25–75% of the forced vital capacity (FVC) ($FEF_{25–75\%}$) according to reference algorithms by STANOJEVIC et al. [25]. The ratio between FEV_1 and FVC (FEV_1/FVC) is reported as a crude ratio.

A methacholine challenge to assess BHR was performed according to international guidelines [26], using a SPIRA dosimeter (Spira Respiratory Care Center Ltd, Hemeenlinna, Finland). The metacholine challenge is reported as positive if the provocative dose of methacholine causing a 20% fall in FEV_1 from baseline (PD_{20}) was f8 mmol (further details are given in the online supplementary material).

Definitions

rBO (at 2 years) was defined as two or more physician-diagnosed episodes or at least one episode lasting o4 weeks. Asthma was defined within each time period (2–10 and 10–16 years) in subjects with a positive response to two or more of the following: doctor-diagnosed asthma, asthma symptoms, and the use of anti-asthmatic medication. BHR was defined as PD_{20} f8 mmol methacholine. Allergic sensitisation was defined as one or more positive SPT o3 mm when compared to the negative control (0.9% NaCl), and asthma symptoms as reporting any episode with heavy breathing, wheezing, chest tightness or dry night-time cough without current cold or lower airway infection.

Determinants and outcomes

The main determinant made at 2 years of age was rBO versus no rBO. Based on the main determinant combined with the presence of asthma criteria at 10–16 years, the following outcomes were defined. Never rBO/asthma: subjects never fulfilling either rBO or asthma criteria; rBO-asthma: rBO subjects fulfilling asthma criteria from 10–16 years; and rBO-remission: rBO subjects not fulfilling asthma criteria from 10–16 years.

Statistical analyses

Continuous variables are presented as mean¡SD for demographic purposes, and otherwise as mean (95% confidence intervals). Categorical variables are presented as counts and percentages. To assess possible differences, Pearson's Chi-squared test was used for categorical variables and t-test for continuous variables. Odds ratios were estimated by binary logistic regression, and effect modification was assessed,

defining .20% change as significant. For statistical analyses SPSS version 15.0 (SPSS, Chicago, IL, USA) was used. Statistical significance was assumed at a level of 5%.

RESULTS

The mean age (minimum–maximum) of the 550 subjects was 10.8 (8.8–12.5) years and 16.7 (15.7–17.5) years at the 10- and 16-year follow-up studies, respectively, with demographic data and family history of allergic disease given in table 1.

Prognosis by asthma classification

The prognosis for the 143 children with rBO at 2 years of age demonstrated that 34% were classified as having asthma in the last period (10–16 years), the majority with asthma presentation in all three periods (23% of all rBO children) whereas 10% had relapsing asthma after 10 years. Remission in terms of asthma definition was observed in 66% of the rBO children, dominated by children going into remission after the 2–10-year period (73%) (fig. 2).

Prognosis by symptoms and signs of asthma activity 10–16 years

Although classified without asthma after 10 years, the rBO-remission group had significantly more frequent use of asthma medication (6.3% versus 0.6%; p,0.001), although few reported use during the last 12 months compared with the never rBO/asthma, whereas asthma symptoms tended, although not statistically significantly, to be more common (27.4% versus 19.3%; p50.09, respectively). Of the adolescents in the rBO-remission group, 32.6% had either symptoms or medication use as opposed to the 19.9% amongst the never rBO/asthma group (p50.009).

BHR was also more frequent in the rBO-remission subjects (20.7% versus 10.2%; p50.008) and, combining these reported and objective findings, 48.4% of the rBO-remission children had at least one of the reported asthma symptoms, asthma medication use or BHR compared with 26.7% of children with never asthma/rBO (p,0.001) (table 2).

Lung function values (FEV_1 % pred, $FEF_{25–75\%}$ % pred and FEV_1/FVC) were significantly reduced in the rBO remission group as well as the rBO asthma group compared with the never asthma groups, but were similar in the rBO groups regardless of asthma status during 10–16 years, both at 10 and 16 years of age (fig. 3 and table 3).

Allergic sensitisation was similar in all three groups at 16 years of age, whereas at 10 years rBO-asthma subjects were more often sensitised to allergens (table 3).

There were no differences in sex within the recurrent bronchial obstruction (rBO)-asthma or -remission groups in reported symptoms or medication use. However, among rBO-remission subjects, more females than males had a positive BHR (30.8% versus 13.2%; p50.04).

Exposure to tobacco smoke (in utero as well as parental indoor smoking until 2 years of age) was not a significant risk factor or confounder of the association of rBO between asthma during 10–16 years (table S3). Even though lung function at birth was not an independent risk factor for asthma outcomes, it significantly modified the association between rBO and later asthma (table S3). The risk estimate of rBO for asthma outcomes during 10–16 years was reduced by 28% by adjusting for lung function at birth.

DISCUSSION

The prognosis of early recurrent bronchial obstruction in our birth cohort study demonstrated that only one-third had persistent asthma throughout childhood and adolescence. However, children with rBO, irrespective of asthma status from 10 to 16 years, had similarly reduced lung function and more frequent BHR at 16 years compared with those with never rBO or asthma. The rBO-remission group more often reported asthma symptoms or use of asthma medication compared with

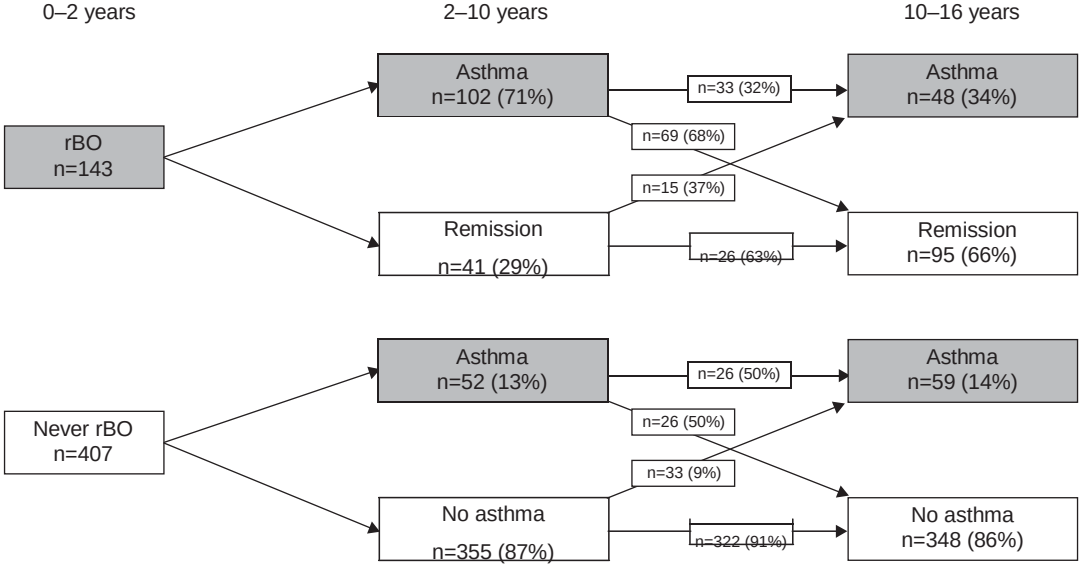

FIGURE 2. Flow chart describing the remission and relapse rates for recurrent bronchial obstruction (rBO) and never rBO subjects with regards to asthma diagnosis through the periods 2–10 years and 10–16 years. Percentages describe the rate either changing or maintaining status concerning asthma between the given periods.

TABLE 2 Symptoms and anti-asthmatic medication usage reported during the interval 10–16 years of age and bronchial hyperresponsiveness (BHR) assessed at 16 years of age

	Never rBO/asthma[#]	rBO-remission 10–16 years	rBO-asthma 10–16 years
Subjects	322	95	48
Asthma symptoms	62 (19.3)	26 (27.4)	48 (100)***
Use of any asthma medication	2 (0.6)	6 (6.3)***	47 (97.9)***
Current[¨] b_2-agonist	0	1 (1.1)	26 (54.2)
Current[¨] ICS/LTRA	1 (0.3)	0	27 (56.3)
b_2-agonist 10–16 years	1 (0.3)	5 (5.3)	15 (31.3)
ICS/LTRA 10–16 years	0	2 (2.1)	10 (20.8)
BHR	32 (10.2)[+]	19 (20.7)[1,**]	11 (24.4)[e,**]
At least one of asthma symptoms or medication	64 (19.9)	31 (32.6)**	48 (100)***
At least one of asthma symptoms, medication or BHR	86 (26.7)	46 (48.4)***	48 (100)***

Data are presented as n or n (%). Asthma symptoms: any reported episode with heavy breathing, wheezing, chest tightness or dry night-time cough without current cold or lower airway infection. BHR is defined as a provocative dose of f8 mmol methacholine causing a 20% fall in forced expiratory volume of 1 s from baseline. rBO: recurrent bronchial obstruction; ICS: inhaled costicosteroid; LTRA: leukotriene receptor antagonist. [#]: reference group; [¨]: within the last 12 months; [+]: n5314; [1]: n592; [e]: n545. All p-values are given compared with children who never fulfilled the rBO or asthma definition. **: p,0.01; ***: p,0.001.

the never rBO/asthma group, and 48.4% of the children in apparent remission still had asthma symptoms, use of asthma medication and/or BHR after 10 years of age. Thus, only one-third of the children with rBO by 2 years of age were found to be without asthma medication, asthma symptoms or BHR by 16 years of age.

Using asthma classification, the 34% of the children with persistent or relapsed disease after rBO at 16 years in the present study is in line with wheeze outcomes in comparable studies; 40% at 10 years from the Isle of Wight, UK [9], 30% at 16 years in the Tucson Respiratory Study [2] and 37% at 13 years in the German Multicenter Allergy study (MAS) [27]. In birth cohorts with a shorter follow-up time (to 5–8 years), persistence of early wheeze varied from about 20% [3, 5] to 40% [28]. Our temporal rBO-asthma phenotypes thus resemble the persistent and early transient wheeze phenotypes in other studies [12], but differ in terms of their using wheeze [2–5, 9, 28] rather than asthma as outcomes.

Exchanging asthma classification with ''wheeze'', 47% of our rBO children had persistent wheeze up to 16 years of age (see online supplementary material), whereas at 10 years ''wheeze ever'' and ''early transient wheeze'' were reported by 30.6% and 8.8%, respectively [1]. The corresponding figures were 40.3% and 20.4%, respectively, in the Isle of Wight study [9]. Approximately one-third of the early wheezers in Oslo were ''transient'' compared with ,50% in the UK study (at 10 years), whereas it is not known what the corresponding results for 16 years would be in the UK study. We required at least two doctor-confirmed episodes of obstructive airway disease where wheeze alone was insufficient to classify the episode as bronchial obstruction. Thus, not only are our classification criteria more conservative than in comparable studies, but we also determined the presence of rBO at 2 years rather than at 3 and 4 years of age [9, 12, 27, 28], highlighting the importance of early-life respiratory events.

All rBO subjects in the present study had reduced lung function at 10 and 16 years of age. The reduced lung function in rBO subjects with persistent or remitting asthma in the present study is in line with findings from the Tucson study at 16 years [2], and the Avon Longitudinal Study of Parents and Children (ALSPAC) [3] and Prevention and Incidence of Asthma and Mite Allergy (PIAMA) [5] studies at 6 years, whereas lung function at 10 years was not impaired among the 139 transient wheezers in the Isle of Wight, UK cohort [9].

BHR was found more frequently in both rBO groups in the present study, in line with findings of the ALSPAC and PIAMA studies [5], and in children with persistent wheeze in other studies [3, 5, 9]. BHR in children with rBO may indicate chronic airway inflammation [29], regardless of active asthma symptoms at the age of 16 years [30], and increases the risk of adulthood disease relapse [31]. The female preponderance for positive BHR amongst rBO-remission subjects has, to our knowledge, not been described previously. However, more BHR in pubertal [32] and adult females compared with males has been reported [33, 34].

Reduced lung function and BHR and in childhood have been associated with adult asthma [8, 13, 14, 31]. Reduced lung function at birth in our study significantly modified the association between rBO and later asthma in the present study. Reduced lung function at birth and at 10 years, as well as BHR at 10 years, all influenced asthma outcomes and may thus suggest an increased risk of adult asthma and possibly also COPD [15, 16]. We found no effect of tobacco smoke exposure *in utero* and up to 2 years of life, which is in line with findings of the MAS study at 13 years [27], but in contrast to results from both the Isle of Wight and the MAS studies at 10 years of age [35, 36] and also into adult age [37], both intrauterine and environmental childhood smoking was associated with reduced lung function and respiratory symptoms.

The rBO-remission children reported more use of asthma medication, although these were small numbers and only a minority reporting current use. The reports of asthma symptoms were not more frequent amongst the rBO-remission children.

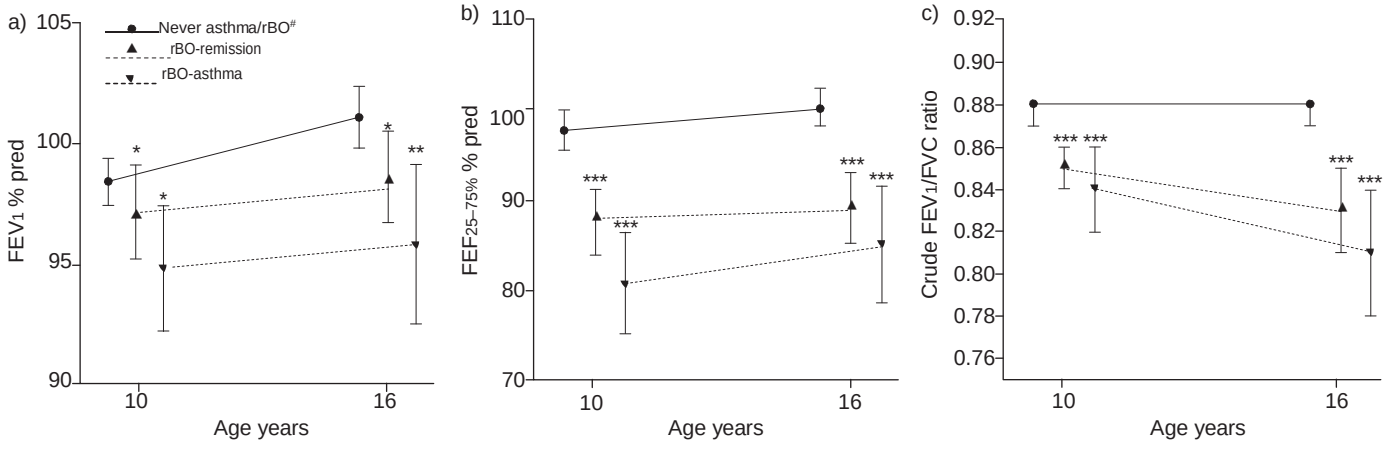

FIGURE 3. Prognosis of recurrent bronchial obstruction (rBO) in terms of lung function. Lung function values are given for a) forced expiratory volume in 1 s (FEV_1), b) forced expiratory flow at 25–75% of the forced vital capacity (FVC) ($FEF_{25–75\%}$), and c) the FEV_1/FVC ratio, given as a crude ratio. All values are given as mean (95% CI). % pred: % predicted. #: reference group. *: p,0.05; **: p,0.01; ***: p,0.001.

Although wheeze symptoms were also reported among never/infrequent wheezers in the statistically derived phenotypes (up to 8 years of age) in the ALSPAC and PIAMA studies [5], it is unclear whether or not this will be associated with asthma in later childhood.

The proportion of children with allergic sensitisation at 16 years was similar in children with rBO and never asthma in the present study, which is in contrast to other articles [2, 3, 5, 9, 27] reporting more often allergic sensitisation in persistent compared with never-wheeze subjects and early transient wheeze [9]. At 10 years, with 26% versus 25.2% of the never asthma and never wheezers, allergic sensitisation was comparable in the ECA and Isle of Wight studies, respectively [1, 9]. The high sensitisation rate at 16 years in the present study also in nonasthmatics, although being remarkable, may obscure the effect of atopy on these subjects.

Strengths and limitations

The prospective design, close follow-up during the first 2 years of life, and thorough characterisation at 10 and 16 years of age are the main strengths of our study, as well as reducing the risk of recall bias. We have chosen to report the findings by relevant period rather than the last year only for each period, as we believe this better reflects the development of the disease. Loss to follow-up between 10 and 16 years of age is unfortunately a common feature of long-term cohort studies of this age [2]. In such cohorts running for a long period of time, there is a risk of overestimating respiratory outcomes. There can be a selection towards those with a previous respiratory diagnosis and also an increased in awareness of symptoms and secondarily increased reporting of symptoms. However, the effect of this potential bias is somewhat reduced by the fact the children attending the 16-year follow-up study were similar in terms of allergic disease or rBO at 10 years compared with those who did not attend the 16-year investigation. Furthermore, the objective documentation is important in a group (adolescents) who often underreport symptoms of disease [38]. With the comparability of asthma phenotypes to other birth cohort studies, we therefore believe that the results of the present cohort are likely to reflect the natural progression of recurrent early wheeze through puberty in a general population.

TABLE 3 Lung function, bronchial hyperresponsiveness and allergic sensitisation at 10 and 16 years of age

	10 years of age			16 years of age		
	Never asthma/rBO	rBO-remission	rBO-asthma	Never asthma/rBO	rBO-remission	rBO-asthma
Subjects n	322	95	48	322	95	48
FEV_1 % pred	98.4 (97.4–99.4)	97.1 (95.2–99.1)*	94.8 (92.2–97.4)*	101.1 (99.8–102.3)	98.1 (96.7–100.5)*	95.8 (92.5–99.1)**
FEV_1/FVC	0.88 (0.87–0.88)	0.85 (0.84–0.86)***	0.84 (0.82–0.86)***	0.88 (0.87–0.88)	0.83 (0.81–0.85)***	0.81 (0.78–0.84)***
$FEF_{25–75\%}$ % pred	97.7 (95.5–99.9)	87.9 (83.9–91.9)***	80.7 (75.3–86.31)***	100.2 (98.2–102.3)	89.0 (85.1–93.0)***	85.1 (78.6–91.5)***
PD_{20} f8 mmol	24.2	37.9*	54.2***	10.2	20.7**	24.4**
Allergic sensitisation	26.4	36.8	41.7*	50.2	55.8	52.1

Data are presented as mean (95% CI) or % unless otherwise stated. The reference is never recurrent bronchial obstruction (rBO)/asthma. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of the FVC; PD_{20}: provocative dose of methacholine causing a 20% fall in FEV_1. *: p,0.05; **: p,0.01; ***: p,0.001.

Conclusion

The prognosis of recurrent bronchial obstruction in the first 2 years of life appears to be good, with only one-third having asthma at 16 years of age. However, children with rBO in remission had reduced lung function, as well as more frequent BHR and use of asthma medication, possibly indicating increased risk of subsequent respiratory disease in adulthood.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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1.1 Asthma with allergic comorbidities in adolescence with allergic comorbidities is associated with bronchial responsiveness and airways inflammation

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Lung function trajectories from birth through puberty reflect asthma phenotypes with allergic comorbidity

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Outcomes of childhood asthma to the age of 50 years

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The association between childhood asthma and adult chronic obstructive pulmonary disease

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ORIGINAL ARTICLE Epidemiology

Asthma with allergic comorbidities in adolescence is associated with bronchial responsiveness and airways inflammation

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adolescence; allergic rhinitis; asthma; atopic dermatitis; bronchial responsiveness; comorbidity; exhaled nitric oxide; gender; phenotype; prevalence

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Abstract

Background: Childhood asthma frequently has allergic comorbidities. However, there is limited knowledge of the longitudinal development of asthma comorbidites and their association to bronchial hyper-responsiveness (BHR) and airway inflammation markers. We therefore aimed to assess the association between childhood asthma with allergic comorbidities and BHR and fractional exhaled nitric oxide (FE_{NO}) and the impact of gender on these associations.

Methods: Based on data from 550 adolescents in the prospective birth cohort 'Environment and Childhood Asthma' study, asthma was defined for the three time periods 0–2, 2–10 and 10–16 years of age, using recurrent bronchial obstruction (rBO) 0–2 years of age as a proxy for early asthma. Asthma comorbidities included atopic dermatitis (AD) and allergic rhinitis (AR) from 10 to 16 years. At age 16 years BHR, assessed by metacholine bronchial challenge, and airway inflammation, assessed by FE_{NO}, were compared between the groups of asthma with or without the two comorbidities, to a reference group with no never asthma, and subsequently stratified by gender.

Results: Boys with asthma and AR, regardless of AD had significantly more severe BHR and higher FE_{NO} than the other asthma phenotypes. Almost half of the children remained in the asthma and AR category from 10 to 16 years, the entire difference being determined by new incident cases from 10 to 16 years.

Conclusions: Asthma phenotypes characterized by allergic comorbidities and AR in particular appears closely associated with BHR and FE_{NO}, especially among boys.

The heterogeneity of childhood asthma (1–3), probably reflecting various underlying pathogenetic mechanisms, challenges our ability to identify clinical meaningful phenotypes that may guide optimal disease prevention and management. The combination of asthma symptoms and allergic comorbidities such as atopic eczema or food allergy is often interpreted as a marker of an increased likelihood of an early asthma debut and longer persistence of asthma symptoms (4).

Two important, but not obligate, childhood characteristics of asthma are non-specific bronchial hyper-responsiveness (BHR) (2, 5) and increased fractional exhaled nitric oxide (FE_{NO}) (6–8). Allergic sensitization, lung function impairment and BHR have been significantly associated with the majority of wheezing phenotypes at 8 years of age (1); however, there is limited knowledge regarding asthma with allergic comorbidities through childhood (6, 9–11).

Boys, more often than girls, have wheezy lower respiratory tract infections and asthma in childhood, with an apparent gender reversion after puberty (2, 12). However, the role of gender in asthma phenotypes, as well as gender impact on their

association with BHR and FE_{NO} through childhood and puberty, needs further clarification.

To understand if asthma phenotypes based on allergic comorbidities is a meaningful way to classify asthma, our primary objective in the present study was to assess whether childhood asthma phenotypes with allergic comorbidities were associated with BHR and FE_{NO} and secondarily to evaluate the impact of gender on these associations. To understand the societal burden of allergic diseases through childhood, we also report the population-based prevalences in the Environment and Childhood Asthma study (ECA) throughout childhood.

Methods and subjects

Design

The present study includes all 550 children from the general population-based prospective birth cohort 'Environment and Childhood Asthma' (ECA) study in Oslo who attended the 16 years follow-up investigation.

From the initial 3754 healthy new-born babies enrolled from 1992 to 1993, for reasons of available resources, we selected for the 10- and 16-year follow-up study all the 802 children who had lung function measured at birth, representative of the general population (13), as well as all children who had attended the nested case–control study at 2 years of age, in total 1215 subjects (3, 5) (Fig. 1).

The study included bi-annual questionnaires completed by the parents from birth to 2 years of age, as well as records (registry cards) of signs of respiratory disease completed by physicians examining the child until 2 years of age.

A 2-year follow-up clinical investigation was performed in a nested case–control study of children with recurrent bronchial obstruction (rBO) (n = 306) and the child born closest in time, but without bronchial obstruction (control), as

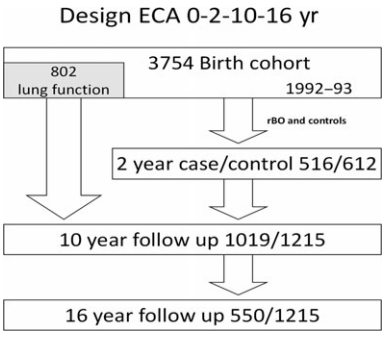

Figure 1 Flow chart of the children included in the 'Environment and Childhood asthma study in Oslo'. Eligibility for the ten and 16 years follow-ups was defined by having performed lung function measurement at birth (n = 802) and/or being part of the 2 years case–control study (recurrent bronchial obstruction (rBO) and controls). Children willing to attend the follow-ups were included. The overall attendance rate at the 10-year follow-up was 84%, while it was 45% at the 16-year follow-up.

described elsewhere (3). The case–control definitions were confirmed by a panel of experienced paediatricians, and at least one episode of bronchial obstruction had to be verified by a doctor (3). Detailed criteria for rBO are given in the online Appendix S1.

The next follow-up studies at ten and 16 years of age included clinical assessments and structured parental (10 years) and respondents (16 years) interviews.

The study was approved by the Regional Medical Ethic Committee and the Norwegian Data Inspectorate and registered in the Norwegian BioBank Registry. Written informed consents were obtained at all investigations.

Subjects

The 550 subjects (52% boys) participating at the 16-year follow-up study (mean age 16.7 years (range 15.7–17.5)) (Table 1) were at birth largely comparable to the entire cohort, with the exception of more often having older siblings, higher family income and more often parental rhinitis ($p = 0.05$). The included subjects were at 10 years shorter, weighed less and had less often AS compared with those who did not attend the 16 year-investigation, but were similar in terms of asthma and allergic disease (3).

Methods

Disease definitions were based upon data from questionnaires, registry cards and doctor's charts data from 0 to 2 years of age, as described in details elsewhere (3), and on structured interview data at 10 and 16 years of age.

Asthma was defined when at least two of the following were present: doctor's diagnosis of asthma, asthma symptoms and use of anti-asthmatic medication.

Allergic rhinitis (AR) was defined as ≥1 of the following reported symptoms in the absence of having a cold; runny nose, blocked nose or sneezing combined with at least one positive SPT and/or sIgE to any of the inhalant allergens tested (see online Appendix S1).

Atopic dermatitis (AD) was defined as reported presence of atopic dermatitis at interview and/or found at clinical investigation at the ten and 16 years investigations.

Markers of asthma severity were based upon number of episodes with asthma symptoms or use of systemic corticosteroids, school absenteeism and the subject's response to the question: 'To what degree has the asthma been bothersome to you in the last year?' (scored from 'severely' to 'not at all') respectively.

Allergic sensitisation (AS) was assessed by skin prick test (SPT) and specific serum immunoglobulin E (sIgE) analyses and considered positive if mean wheal diameter of the SPT was ≥3 mm larger than the negative control (NaCl) and/or sIgE ≥0.35 kU/l, respectively.

Lung function was assessed by maximally forced expiratory flow-volume loops according to European guidelines (14) using a Sensormedics V-max (Sensormedics Diagnostics, Yorba Linda, CA, USA) spirometer. Values are reported as percentage predicted according to Stanojevic et al. (15).

Table 1 Characterstics of the study population from the ten (n = 540) and 16 years (n = 550) follow-up investigations

		Age (years)	Asthma (n = 106/107)	Asthma in remission (n = 121/121)	Never asthma (n = 313/322)
Gender (male)	N (%)		62 (57.9)	53 (43.8)	167 (51.9)
Height	Mean (SD)	10	144.4 (7.5)	144.2 (7.3)*	145.9 (7.7)
	Mean (SD)	16	173.8 (7.7)	173.6 (8.1)	172.4 (8.8)
Weight	Mean (SD)	10	37.3 (7.4)	37.7 (7.6)	38.1 (7.8)
	Mean (SD)	16	65.9 (9.7)	67.5 (11.4)	65.1 (11.6)
FEV_1%	Mean (SD)	10	95.6 (9.3)**	96.3 (9.5)*	98.4 (8.9)
	Mean (SD)	16	97.9 (12.2)*	97.6 (11.6)**	101.1 (11.5)
FE_{NO} (ppb)	GM (SD)	10	8.96 (2.28)***	6.63 (1.70)	6.03 (1.79)
	GM (SD)	16	13.88 (2.26)*	11.14 (1.66)	11.66 (1.74)
PD_{20} (lmol)	GM (SD)	10	3.82 (5.96)***	9.45 (3.17)*	12.57 (2.66)
	GM (SD)	16	10.06 (3.33)***	15.33 (2.14)	17.36 (1.97)
Allergic rhinitis	N (%)	10	36 (34)***	8 (6.6)	24 (7.7)
	N (%)	16	53 (49.5)***	26 (21.5)	66 (20.5)
	N (%)	0–10	39 (36.4)***	9 (7.4)	26 (8.1)
	N (%)	10–16	53 (49.5)***	26 (21.5)	67 (20.8)
Atopic dermatitis	N (%)	10	37 (34.9)***	35 (28.9)**	52 (16.6)
	N (%)	16	20 (18.7)	18 (14.9)	37 (11.5)
	N (%)	0–10	56 (52.8)***	53 (43.8)**	93 (29.7)
	N (%)	10–16	26 (24.3)	23 (19.0)	53 (16.5)
Allergic sensitization	N (%)	10	55 (51.9)***	41 (33.9)	85 (27.2)
		16	67 (62.6)*	66 (54.5)	161 (50.3)
ICS use	N (%)	0–10	56 (52.8)***	38 (31.4)***	1 (0.3)
	N (%)	10–16	76 (71.0)***	2 (1.7)*	0
Tobacco exposure	N (%)	0–10	16 (15.0)	22 (18.2)	45 (14.0)
Second hand smoke	N (%)	10–16	12 (11.2)	23 (19.0)	44 (13.7)
Personal smoking	N (%)	10–16	16 (15.0)	16 (13.3)	37 (11.5)
in utero	N (%)		29 (27.1)	32 (26.4)	72 (22.4)
Parental asthma	N (%)	16	26 (24.3) ***	9 (7.4)	34 (10.6)
Hayfever	N (%)	16	44 (44.1) **	38 (31.4)	89 (27.6)

Phenotype classifications and analyses include the 107 subjects with asthma from 10 to 16 years, compared with those with never asthma (reference group). The 121 subjects with previous, but no longer symptoms or medication for asthma from 10 to 16 years (asthma in remission) are shown separately and included in analyses of stability of phenotypes through childhood. Ten subjects participating at 16 years only (one with asthma, nine with never asthma).

*p < 0.05; **p < 0.01; ***p < 0.001 Parental disease is reported as the presence of disease in at least one of the parents, Tobacco smoke exposure; reported smoking in the home (reported by parents at 10 years and by subject at 16 years), ICS: inhaled corticosteroids.

GM: Geometric mean.

Bronchial hyperresponsiveness was assessed by a metacholine bronchial challenge using tidal inhalation of doubling metacholine doses from a SPIRA® dosimeter (Spira Respiratory Care Center Ltd, Hemeenlinna, Finland), reporting the cumulative metacholine dose causing 20% reduction in FEV_1 (PD_{20}) or reaching the maximum cumulative metacholine dose of 22.4 lmol (4.4 mg), according to American Thoracic Society (ATS) recommendations (16).

Fractional exhaled nitric oxide (FE_{NO}) was measured by single breath technique according to ATS/ERS guidelines (17) using an EcoMedics Exhalyzer ® CLD 88sp with DENOX 88 (ECO MEDICS AG, Duernten, Switzerland). Prior to the investigations the subjects were without symptoms or signs of respiratory tract infection for at least 4 weeks, withhelding relevant medications (see online Appendix S1) as appropriate.

Asthma comorbidity phenotypes were constructed by the presence of defined asthma at 10–16 years of age (n = 107) combined with the presence or absence of allergic rhinitis (AR) and/or atopic dermatitis (AD) from 10 to 16 years (Fig. 2).

Allergic rhinitis (AR) was chosen rather than rhinitis to more precisely target allergic comorbidities (9).

Subjects with rBO and asthma before 10 years of age only were classified as asthma in remission, with the corresponding allergic comorbidities reported for assessing stability of the asthma phenotypes. Subjects without previous rBO or asthma (n = 322) were classified as never asthma and defined as the reference group.

Population-based prevalence estimates for asthma and allergic diseases were categorized as active, denoting presence of symptoms and/or use of medication during last 12 months,

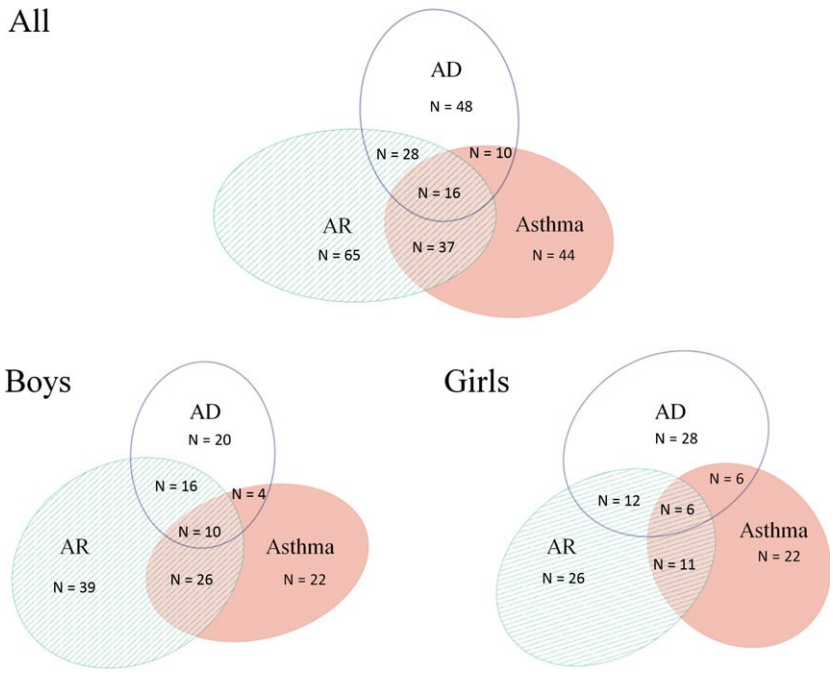

Figure 2 Description of the Asthma Comorbidity Phenotype (ACP). The allergic diseases, asthma, allergic rhinitis (AR) and atopic dermatitis (AD) from ten to 16 years of age (n = 107) are presented as a Venn diagram (eulerAPE, University of Kent, UK) with areas being proportional to prevalence. Significantly, more boys than girls had asthma and allergic rhinitis.

and ever, having been classified with the diagnosis in the study at any time from birth. Clinical definitions are given in detail in the online Table S1.

The main outcomes are the associations between PD_{20} and FE_{NO} and the asthma comorbidity phenotypes defined from 10 to 16 years.

Statistical analyses

Continuous variables are presented as mean with standard deviation SD (demographic data) or 95% confidence intervals (CI) and categorical data as counts and percentages. For PD_{20} and FE_{NO} measurements, log transformation was performed to reach normal distribution and data are presented as geometric means. To assess possible differences, Pearson's chi square-test was used for categorical variables, and Student's t-test for continuous variables. Analysis of variance was used to assess differences between the phenotypes and Tukey's test to assess specific differences within the asthma comorbidity phenotypes. Children who did not reach a significant fall in FEV_1 were assigned the maximal PD_{20} value of 22.4 lmol. The 15 subjects who did not perform metacholine challenge, one due to low FEV_1%, were not entered into the analyses for BHR.

Population-based prevalence rates were calculated based on the entire cohort (n = 3754) at 2 years of age. At 10 and 16 years of age, all subjects with lung function measured at birth were regarded as originating from a general population. Accordingly, prevalences at 10 years of age were calculated based on the 616 of these 802 children (11) who attended the 10-year visit. At 16 years, however, prevalence rates were estimated for all 550 by calculating adjusted prevalences according to Fleiss' indirect standardization procedure (18), weighting the subjects according to the group from which they originated. Alas, all subjects who had lung function measured at birth were weighted as a general population, whereas the children from the nested case–control study at two years were weighted accordingly.

For statistical analyses Statistical Package for Social Sciences Version 15.0 (SPSS, Chicago, IL, USA), was used. Statistical significance was assumed at a level of 5%.

To create Venn diagrams we used eulerAPE® (University of Kent, UK, www.eulerdiagrams.org/eulerAPE).

Results

Asthma comorbidity phenotypes

At least one allergic comorbidity was present in 63 (58.9%) of the 107 subjects with asthma from 10 to 16 years. The most common asthma phenotype was asthma alone (41.1%) followed by asthma with allergic rhinitis (34.6%), asthma with allergic rhinitis and atopic dermatitis (15.0%) and asthma with atopic dermatitis (9.4%) only, respectively (Fig. 2). The asthma phenotypes did not differ significantly in terms of markers of asthma severity or in the use of anti-inflammatory medication (Table 2). Gender was significantly associated with one asthma phenotype only; more boys than girls suffered from asthma and AR (12.0% versus 5.2%, respectively, p = 0.01).

Lung function and BHR were significantly associated with asthma phenotypes, with the lowest FEV_1% in subjects with asthma, AR and AD (Table 2), significant, however, in boys only after gender stratification. Subjects with asthma and AR, regardless of AD, had significantly lower PD_{20} compared with the reference group (both $p \leq 0.001$) (Fig. 3), but the associations were significant in boys only after sex stratification (<0.001 for both) (Table 2).

Table 2 Clinical characteristics of asthma and allergic rhinitis reported at 16 years of age and objective measures of asthma assessed at 16 years of age are presented as mean (95 percentage confidence intervals) for continuous variables and as counts and percentages for dichotomous variables

	N	Never asthma 322	Asthma 44	Asthma, AD 10	Asthma, AR 37	Asthma, AD, AR 16	p-value
Boys	N (%)	155 (48.1)	22 (50)	4 (40)	26 (70.3)	10 (62.5)	0.10
Asthma							
Bothersome*	Mean (95% CI)		5.67 (5.33, 6.02)	6.00 (5.42, 6.58)	5.38 (4.95, 5.80)	5.13 (4.35, 5.90)	0.22
Symptom episodes†	Mean (95% CI)		1.43 (1.05, 1.81)	1.44 (0.42, 2.47)	1.49 (1.12, 1.85)	1.75 (1.06, 2.44)	0.84
School abseintism‡	Mean (95% CI)		1.07 (0.90, 1.23)	1.10 (0.87, 1.33)	1.17 (0.95, 1.39)	1.07 (0.92, 1.21)	0.86
Use of ICS	N (%)		20 (45.5)	3 (30.0)	20 (54.1)	6 (37.5)	0.48
Allergic rhinitis							
Bothersome*	Mean (95% CI)	4.73 (4.34, 5.11)			4.54 (3.91, 5.17)	4.27 (3.47, 5.06)	0.59
Limit daily activities§	Mean (95% CI)	2.03 (1.79, 2.27)			1.92 (1.62, 2.21)	2.13 (1.65, 2.60)	0.73
FEV_1%	Mean (95% CI)	101.1 (99.8, 102.3)	99.0 (94.8, 103.2)	101.0 (95.7, 106.2)	99.7 (96.1,103.3)	88.9 (84.0, 93.8)	0.002
♂		100.1 (98.4, 101.7)	95.2 (89.8, 100.6)	99.2 (91.5, 106.9)	99.8 (95.2,104.4)	86.2 (78.6, 93.8)	0.001
♀		102.0 (100.1, 104.0)	102.7 (96.3, 09.2)	102.2 (92.9, 111.4)	99.6 (93.0, 106.1)	93.3 (89.7, 97.0)	0.507
Allergic sensitization	Percentage	161 (50.3)	10 (22.7)	4 (40.0)	37 (100.0)	16 (100.0)	
♂		85 (55.2)	6 (27.3)	1 (25.0)	26 (100.0)	18 (100.0)	
♀		76 (45.8)	4 (18.2)	11 (50.0)	11 (100.0)	6 (100.0)	
PD_{20} (lmol)	GM (95% CI)	17.4 (16.1, 18.7)	13.2 (9.8, 22.0)	18.3 (14.8, 22.7)	7.0 (4.4, 11.1)	7.1 (3.1, 16.1)	<0.001
♂		18.7 (17.1, 20.3)	11.7 (7.0, 19.6)	21.8 (20.0, 23.8)	5.9 (3.2, 10.9)	3.6 (1.0, 16.6)	<0.001
♀		16.2 (14.3, 18.3)	14.9 (10.5, 21.2)	16.3 (11.3, 23.5)	10.4 (5.3, 20.4)	17.1 (12.5, 23.5)	0.475
FE_{NO} (ppb)	GM (95% CI)	11.7 (11.0, 12.4)	8.9 (7.6, 10.4)	10.6 (7.6, 14.9)	20.8 (15.6, 27.8)	22.4 (13.9, 36.4)	<0.001
♂		12.9 (11.7, 14.1)	10.5 (8.2, 13.5)	10.0 (5.2, 19.2)	25.8 (17.9, 37.3)	34.3 (17.5, 67.1)	<0.001
♀		10.6 (9.8, 11.5)	7.5 (6.3, 9.0)	11.1 (6.3, 19.5)	12.5 (9.0, 17.4)	11.9 (8.6, 16.4)	0.028

All variables are given in relation to exclusive asthma phenotypes in 429 adolescents at 16 years of age, and the clinical characterisitics are reported for the 12 months prior to investigation. Allergic rhinitis related data from the 67/322 subjects with allergic rhinitis among the never asthma group are presented.

GM: Geometric mean. ICS: reported use of inhalation steroid in the last 14 days. LTRA: reported use of leukotrieneantagonists in the last 14 days.

*Reported bothersome disease from 1 to 7 (1: severely to 7:not at all).

†Reported number of episodes with asthma symptoms where 0: none, 1: 1–3, 2: 4–12 and 4: >12.

‡Asthma related absence from school where 1: none, 2: <5 days, 3: 5–10 days and 4 >12 days.

§Degree of influence the allergic rhinitis symptoms had on daily activities where 1: none, 2: minor, 3: moderate and 4: substantial. FEV_1%: percentage predicted value of the forced expiratory volume after 1 s. PD_{20}: cumulative dose of metacholine causing a 20% reduction of FEV_1. FE_{NO}: fraction of exhaled nitric oxide. For FEV_1% six was missing, all from the never asthma phenotype, for PD_{20} 11 was missing, eight from never asthma, one from asthma+AR and two from asthma+AD+AR. FE_{NO} was missing five subjects; four from the never asthma group and one from asthma+AD+AR. Missing values are non-applicable.

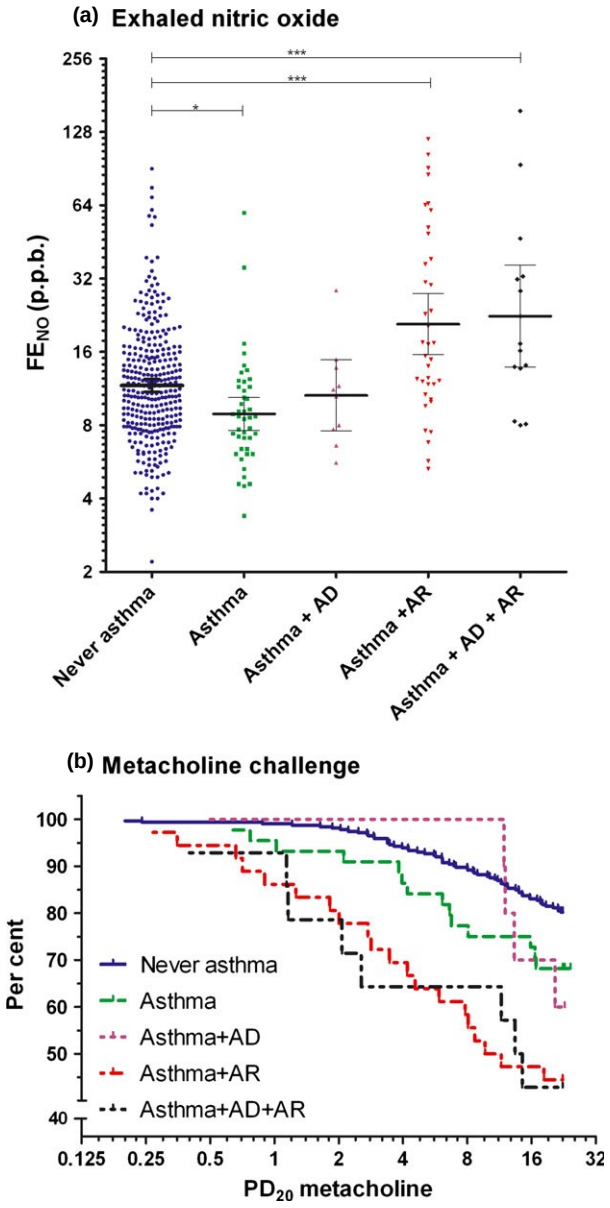

Figure 3 (a) Scatter plot of fractional exhaled nitric oxide (FE_{NO}) for the asthma comorbidity phenotypes with geometric means and 95% confidence intervals shown in the plots. Significant differences between the phenotypes and the never asthma subjects are indicated as follows *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. (b) Kaplan –Meier plot describing the proportion of children with reduction >20% of FEV_1% in relation to inhaled dose of metacholine (PD_{20}) for the asthma comorbidity phenotypes. There were significant differences between the phenotypes (log-rank test $p < 0.0001$).

FE_{NO} was significantly increased in subjects with asthma accompanied by AR or AD compared with the reference group ($p = 0.018$ to $p < 0.001$) (Table 2 and Fig. 3), but in boys only after gender stratification ($p = 0.043$-$p < 0.001$).

The associations with FE_{NO}, BHR and FEV_1% remained significant after stratification for the use of ICS in the last 12 months and the last 14 days (all values <0.005)(online Table S2). Due to small groups further stratification for gender was not performed.

Stability of asthma phenotypes through childhood

Twenty-one subjects (34%) were defined with asthma after 10 years of age only, whereas in 42% the same asthma phenotype was observed at both 10 and 16 years (Fig. 4). The greatest stability was observed for the asthma and AR (± AD) phenotype where all 30 subjects who had these diseases at ten years of age, still had them at 16 years. There was an influx of 23 subjects from 10 to 16 years, and of all 53 subjects with asthma and AR at 16 years, 20 (37.7%) also had rBO at 2 years, half of whom also had AD. In the 26 subjects with Asthma and AD (± AR) at 10 to 16 years of age, 6 (23.0%) had rBO and AD at 2 years and 17 (65.4%) had asthma and AD at 10 years of age (Fig. 4). The subjects with never asthma from 0 to 10 years, having incident asthma with either AD or AR from 10 to 16 years, had significantly lower PD_{20} at 10 years compared with those with a stable never asthma phenotype from 0 to 16 years. Otherwise, there were at 10 years of age no differences in associations between those with stable and change in asthma comorbidity phenotype in FEV_1 or FE_{NO} (results not shown).

The presence of AD and AR was significantly more common during both time periods (0–10 and 10–16 years) in subjects with asthma compared to subjects with asthma in remission and those without asthma (Table 1) at 16 years. The presence of AR, however, was similar among subjects with asthma in remission and those with never asthma at both time periods (Table 1).

Compared to never asthma, subjects with asthma and asthma in remission had significantly lower FEV_1%, whereas FE_{NO} and PD_{20} were significantly higher among those with asthma only (Table 1).

Allergic sensitisation, present in 62.6% of subjects with asthma from 10 to 16 years of age, was not significantly different in boys and girls (69.4 vs 53.3%, $p = 0.09$, respectively), and not significantly associated with lung function, BHR or use of anti-inflammatory medication (online Table S3). The FE_{NO} levels were, however, significantly higher among subjects with asthma who were sensitised compared with no AS in all (mean (95CI) 16.19 (13.58, 18.80) vs. 9.09 (1.55, 6.02) ppb, $p = 0.0009$)), as well as in boys and girls (online Table S3).

Population based prevalences of allergic diseases through childhood

At 16 years of age, the prevalences of active asthma, asthma ever and AS were 13.7%, 26.4% and 52.6%. Active allergic rhinitis and AD was observed in 25.6% and 13.6%, respectively. Boys, more often than girls, had rBO and AD at 2 years, all active allergic diseases and AS at 10 years, and active AR and AS at 16 years (Fig. 5 and online Table S4).

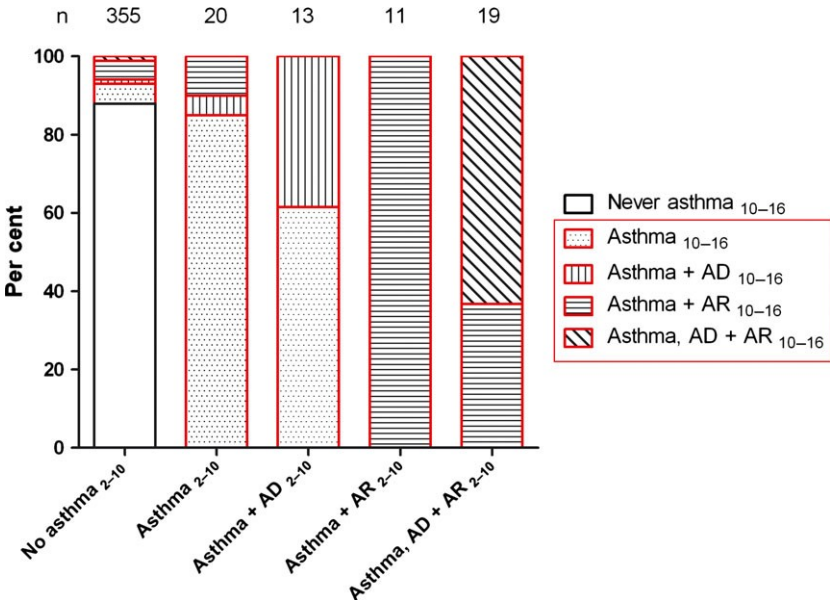

Figure 4 Bar chart describing the stability of the asthma comorbidity phenotype from ten to 16 years of age. Each bar denotes phenotype at 10 years, and the contents of the bar indicate corresponding categorizations at 16 years of age. The figure describes the stability of the asthma phenotypes with allergic rhinitis (AR), with no remission of allergic rhinitis. For atopic dermatitis (AD), there was remission from ten to 16 years of age.

Discussion

The majority (58.5%) of post-pubertal subjects with current asthma (prevalence 13.7%) had at least one of the allergic comorbidities allergic rhinitis and/or atopic dermatitis. The combination of asthma with AR, regardless of AD, was most closely associated with reduced lung function and increased BHR and FE_{NO}. The asthma phenotype with AR was relatively stable, with influx only of asthma from ten to 16 years of age, with similar phenotype associations with lung function as well as FE_{NO} in subjects with stable or changing phenotypes from 10 to 16 years.

The present distribution of phenotypes were similar to those reported in the Swedish BAMSE cohort at 12 years of age (10), and the observed associations between asthma comorbidity phenotypes with AR independent of AD are supported by previous reports on increased FE_{NO} at 14 years of age related to male gender, wheeze, rhinoconjunctivitis, but not to rash (6). The present increase in BHR and reduced lung function in subjects with asthma and AR is also in line with previous reports (19–21).

The more pronounced increase in FE_{NO} and BHR among subjects with asthma and AR, regardless of AD, are in line with the hypothesis of 'one airway, one disease' (19). The presence of BHR indicates airways inflammation and airway remodelling (22), whereas increased FE_{NO} is observed in asthma AD, AR (23, 24) as well as in males (25), indicating eosinophilic airway inflammation (26). We are aware of only one case–control study from China (24) in 10-year olds using the exact same phenotype approach, which supports the present increased FE_{NO} in asthma with AR as well as in asthma with AR and AD. In contrast to the present study, however, they reported significantly increased FE_{NO} also in subjects with asthma and AD, as has also been reported elsewhere (11).

Similar to other population-based studies (7, 27), we found an overlap in both BHR and FE_{NO} including increased FE_{NO} and BHR in subjects with never asthma (Fig. 3 and online figure S1). The low FE_{NO} values in our children with asthma only may reflect less allergic sensitization in this phenotype, in line with reports from the Isle of Wight birth cohort study (IOWBC) at 18 years of age (7) and also the ECA study at 10 years (8).

The presently reported prevalences of allergic diseases and allergic sensitisation are similar to those reported from the IOWBC at 18 years (28–30), pointing to heavy societal burden (Fig. 4) and a significant personal burden with complex allergic diseases affecting 60% of the post-pubertal subjects with asthma. The present findings of increased airways inflammation (FE_{NO}) and BHR in subjects with both asthma and allergic rhinitis support the necessity of early diagnosis and treatment of both diseases, as pointed out in the ARIA guidelines (19) to improve disease control and quality of life. Our data suggest that comorbid allergic diseases, objective measures as well as gender should be included in future randomized paediatric clinical trials to provide further insight into individual treatment.

The stability of asthma phenotypes in approximately 50% from 10 to 16 years in the asthma phenotypes of those with asthma and AR questions the reliability of early assessments (pre-puberty) for identification of potential mechanisms underlying asthma phenotypes but is supported by recent reports from a large study in birth cohorts at 4 and 8 years (31).

The phenotypes in the present study were similar in terms of markers of asthma severity, most having mild asthma with only 45.8% reporting use of ICS in the last 12 months. Thus, speculations that the associations with lung function, BHR and FE_{NO} may be more related to comorbidities than with severity of asthma must be viewed with caution.

Strengths and limitations

The longitudinal prospective design and the careful characterization including objective measures from birth to 2 years, at

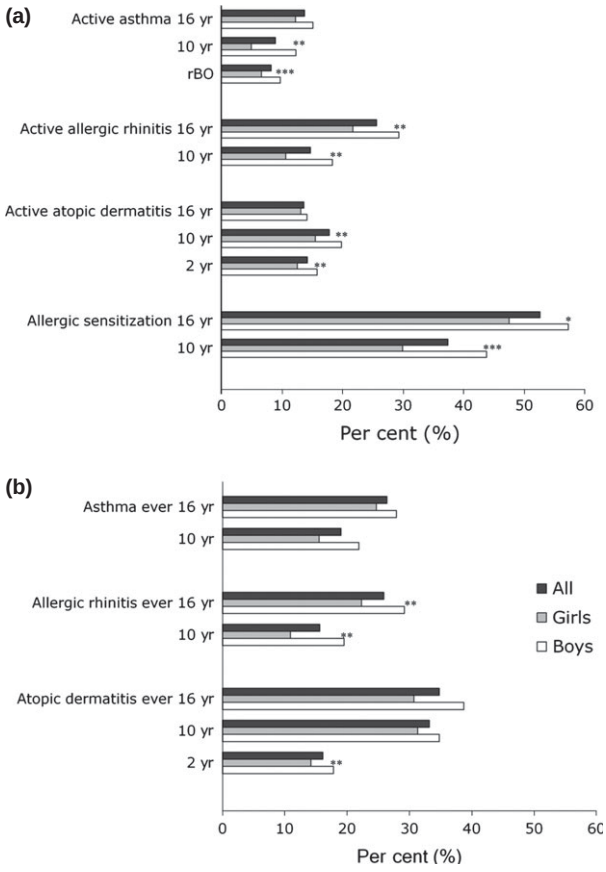

Figure 5 Prevalence of asthma, atopic diseases and allergic sensitization at two, ten and 16 years of age, presented as percentage. Active denotes symptoms or other signs of disease during the last 12 months prior to investigation, whereas ever denotes lifetime presence. The prevalence at 2 years are based on the original ECA cohort (n = 3754), whereas the prevalence at 10 years are based on the 616 subjects originating from the randomly included lung-function-cohort (n = 802) at birth. At 16 years adjusted prevalence are presented (n = 550) (see statistics).

10 and 16 years, strengthen the study, although recall bias at 10 and 16 years and substantial loss to follow-up may bias our results. However, limited skewing towards allergic disease was observed (3); thus, we believe that the observed associations between asthma phenotypes and objective findings are justified.

The indicator of early obstructive airways disease, rBO, has previously been associated with reduced lung function (3). Our asthma definition after 2 years of age was previously reported to be reflected in objective measures (lung function and bronchial hyper-responsiveness) (5).

Due to a relatively limited size of the study population, the number of subjects within some phenotypes was small, limiting our ability to conclude on negative findings.

Conclusion

Asthma through puberty was accompanied by allergic rhinitis and/or atopic dermatitis in almost 60 percentage, and asthma phenotypes with allergic rhinitis through puberty appeared most closely associated with BHR and FE_{NO}. The associations were mainly found among boys suggesting that asthma and combinations of allergic comorbidities may represent a gender-related phenotype.

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Conflict of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Scatter plots of the cumulative dose of metacholine causing at least 20% reduction in lung function (PD_{20}) for the phenotypes within the asthma comorbidity approach.

Figure S2. The influx, outflux and also relapse (*) respectively of atopic dermatitis (AD) (left) from 2-10 and 10-16 years are described with arrows, with the corresponding influx from 10-16 years given for allergic rhinitis (AR).

Table S1. Definitions of the outcomes in the present study.

Table S2. Associations between the asthma phenotypes stratified for reported use of inhaled corticosteroids (ICS) within the last 12 months and 14 days, respectively.

Table S3. Characteristics and comparisons of subjects with asthma and allergic sensitisation (allergic asthma) and asthma without allergic sensitisation, in terms of forced expiratory volume in 1 s, exhaled nitric oxide (FENO) og metacholine challenge test (PD20).

Table S4. Prevalences of asthma, atopic diseases and allergic sensitisation at 2, 10 and 16 years of age are given for all subjects in table E2A, and by girls and boys in table E2B with significant sex difference given by *.

Table S5. The association at 16 years of age between the allergic diseases allergic rhinitis (AR) and atopic dermatitis (AD) with lung function by FEV_1%, BHR and exhaled nitric oxide (PD_{20} and FE_{NO}, respectively) are given for the 322 subjects who never had recurrent bronchial obstruction (rBO) and/or asthma (reference group) in table E4A and for the 121 subjects with asthma in remission after 10 years of age. Due to small numbers in the rBO/asthma remission group, p-values are not presented.

Appendix S1. Methods.

6.6 Astma og allergi som nasjonal utfordring

Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985–2008

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The geography of chronic obstructive pulmonary disease: A population-based study of Norway

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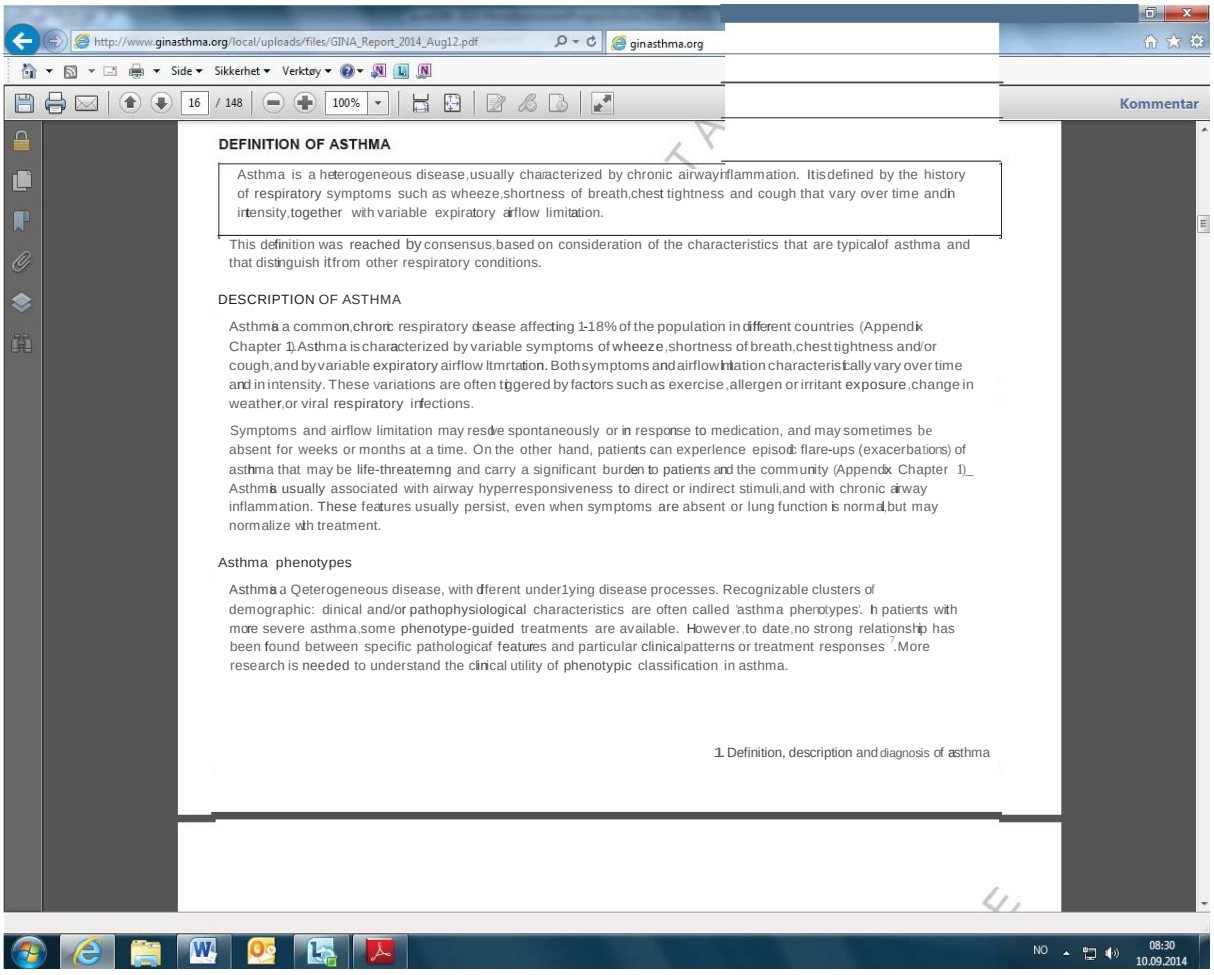

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Kommentar

DEFINITION OF ASTHMA

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

This definition was reached by consensus, based on consideration of the characteristics that are typical of asthma and that distinguish it from other respiratory conditions.

DESCRIPTION OF ASTHMA

Asthma is a common, chronic respiratory disease affecting 1-18% of the population in different countries (Appendix Chapter 1). Asthma is characterized by variable symptoms of wheeze, shortness of breath, chest tightness and/or cough, and by variable expiratory airflow limitation. Both symptoms and airflow limitation characteristically vary over time and in intensity. These variations are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory infections.

Symptoms and airflow limitation may resolve spontaneously or in response to medication, and may sometimes be absent for weeks or months at a time. On the other hand, patients can experience episodic flare-ups (exacerbations) of asthma that may be life-threatening and carry a significant burden to patients and the community (Appendix Chapter 1). Asthma is usually associated with airway hyperresponsiveness to direct or indirect stimuli, and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment.

Asthma phenotypes

Asthma is a heterogeneous disease, with different underlying disease processes. Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'. In patients with more severe asthma, some phenotype-guided treatments are available. However, to date, no strong relationship has been found between specific pathological features and particular clinical patterns or treatment responses [7]. More research is needed to understand the clinical utility of phenotypic classification in asthma.

1. Definition, description and diagnosis of asthma

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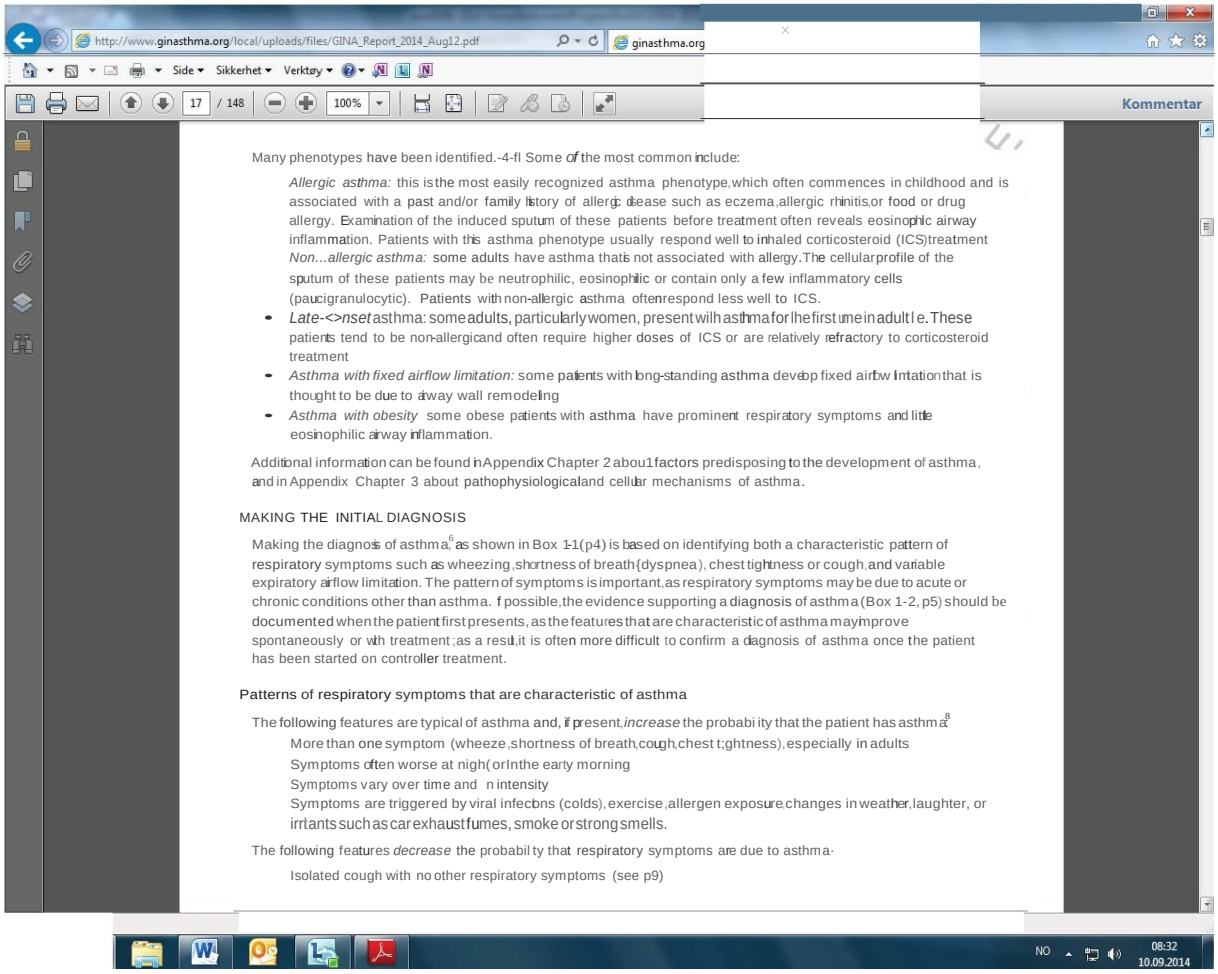

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17 / 148 100%

Kommentar

Many phenotypes have been identified.-4-fl Some of the most common include:

Allergic asthma: this is the most easily recognized asthma phenotype, which often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation. Patients with this asthma phenotype usually respond well to inhaled corticosteroid (ICS) treatment
Non...allergic asthma: some adults have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells (paucigranulocytic). Patients with non-allergic asthma often respond less well to ICS.

- *Late-<>nset* asthma: some adults, particularly women, present with asthma for the first time in adulthood. These patients tend to be non-allergic and often require higher doses of ICS or are relatively refractory to corticosteroid treatment
- *Asthma with fixed airflow limitation:* some patients with long-standing asthma develop fixed airflow limitation that is thought to be due to airway wall remodeling
- *Asthma with obesity* some obese patients with asthma have prominent respiratory symptoms and little eosinophilic airway inflammation.

Additional information can be found in Appendix Chapter 2 about factors predisposing to the development of asthma, and in Appendix Chapter 3 about pathophysiological and cellular mechanisms of asthma.

MAKING THE INITIAL DIAGNOSIS

Making the diagnosis of asthma,[6] as shown in Box 1-1 (p4) is based on identifying both a characteristic pattern of respiratory symptoms such as wheezing, shortness of breath (dyspnea), chest tightness or cough, and variable expiratory airflow limitation. The pattern of symptoms is important, as respiratory symptoms may be due to acute or chronic conditions other than asthma. If possible, the evidence supporting a diagnosis of asthma (Box 1-2, p5) should be documented when the patient first presents, as the features that are characteristic of asthma may improve spontaneously or with treatment; as a result, it is often more difficult to confirm a diagnosis of asthma once the patient has been started on controller treatment.

Patterns of respiratory symptoms that are characteristic of asthma

The following features are typical of asthma and, if present, *increase* the probability that the patient has asthma[8]

More than one symptom (wheeze, shortness of breath, cough, chest tightness), especially in adults
Symptoms often worse at night or in the early morning
Symptoms vary over time and in intensity
Symptoms are triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter, or irritants such as car exhaust fumes, smoke or strong smells.

The following features *decrease* the probability that respiratory symptoms are due to asthma:

Isolated cough with no other respiratory symptoms (see p9)

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