

Forebygging av allergi hos barn

Notat fra Kunnskapsenteret
Systematisk litteratusøk med
sortering
September 2012

 kunnskapsenteret

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Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Kunnskapssenteret er formelt et forvaltningsorgan under Helsedirektoratet, men har ingen myndighetsfunksjoner og kan ikke instrueres i faglige spørsmål.

Nasjonalt kunnskapssenter for helsetjenesten
Oslo, september 2012

Hovedfunn

Nasjonalt kunnskapssenter for helsetjenesten har, basert på bestilling fra Helsedirektoratet, utført et systematisk litteratursøk etter oppsummert kunnskap med påfølgende sortering av mulig relevante publikasjoner. Oppdraget ble løst ved å finne oppsummert litteratur/forskning om forebygging av ulike typer allergier hos barn.

Metode

Vi utarbeidet søkestrategi for et systematisk litteratursøk. Det ble søkt i medisinske databaser etter systematiske oversikter om forebygging av allergi hos barn. Søket ble utført i juli 2012 og tidsbegrenset bakover i tid til 2009. To prosjektmedarbeidere gikk uavhengig av hverandre gjennom identifiserte publikasjoner/referanser og vurderte relevans i forhold til inklusjonskriteriene.

Resultater

Vi identifiserte totalt 450 referanser. Av disse ble 81 vurdert som mulig relevante. Vi har delt dem inn i fem grupper etter faktorer som utløser allergien.

- 4 oversikter omfattet retninglinjer, andre mulige forklaringsfaktorer og betydning av geografisk område
- 17 oversikter omfattet faktorer knyttet til genetiske forhold og foreldrenes sykdom og handlinger
- 13 oversikter omfattet faktorer knyttet til barnet sykdomshistorie
- 24 oversikter omfattet faktorer knyttet til barnets ernæring
- 22 oversikter omfattet faktorer knyttet til barnets omgivelser

Tittel:

Forebygging av allergi hos barn

Publikasjonstype:

Systematisk litteratursøk med sortering

Systematisk litteratursøk med sortering er resultatet av å

- søke etter relevant litteratur ifølge en søkestrategi og
- eventuelt sortere denne litteraturen i grupper presentert med referanser og vanligvis sammendrag

Svarer ikke på alt:

- Ingen kritisk vurdering av studienes kvalitet
- Ingen analyse eller sammenfatning av studiene
- Ingen anbefalinger

Hvem står bak denne publikasjonen?

Kunnskapssenteret har gjennomført oppdraget etter forespørsel fra Helsedirektoratet

Når ble litteratursøket utført?

Søk etter studier ble avsluttet Juli 2012.

Key messages

Norwegian Knowledge Center for the Health Services was commissioned by the Norwegian Directorate of Health to perform a systematic literature search for systematic reviews examining interventions to prevent various types of allergies in children.

Method

We performed a systematic search in various medical databases for systematic reviews about interventions to prevent of allergy in children. The search was performed in July 2012 and was limited to the period 2009-2012. Both authors screened the identified references for relevance in accordance with the inclusion criteria.

Results

We identified 450 unique references in total. Of these 81 were considered potentially relevant for prevention of allergy in children. We arranged the references into five groups according to which factors that might be the cause the allergy.

- 4 reviews was about guidelines, other possible confounders and the importance of geographical area
- 17 reviews was about factors related to genetic disposition and the illnesses and actions of the parents
- 13 reviews was about factors related to the child's history of illnesses
- 24 reviews was about factors related to the nutrition of the child
- 22 reviews was about factors related to the environment of the child.

Title:

Prevention of allergy among children

Type of publication:

Systematic reference list

A systematic reference list is the result of a search for relevant literature according to a specific search strategy. The references resulting from the search are then grouped and presented with their abstracts.

Doesn't answer everything:

- No critical evaluation of study quality
- No analysis or synthesis of the studies
- No recommendations

Publisher:

Norwegian Knowledge Centre for the Health Services

Updated:

Last search for studies: July 2012.

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Forord

Kunnskapssenteret mottok en bestilling fra Helsedirektoratet ved divisjonsdirektør Knut-Inge Klepp om en oppsummering om forebygging av allergi hos barn.

Bakgrunnen for bestillingen er at Nasjonal Strategi for forebygging og behandling av astma og allergisykdommer 2008-2012 har som mål å stanse utviklingen, og gradvis redusere forekomsten av astma og allergi, spesielt hos barn under 12 år. Dagens tall viser at vi ikke har klart å nå dette målet. Beklageligvis ser det ut til at det fortsatt er en økning av astma og allergi hos barn. Det foregår forskning på området både nasjonalt og internasjonalt. Vet vi hva som virker?

Prosjektgruppen har bestått av:

- Hilde H. Holte, seniorforsker, Kunnskapssenteret
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Innledning

Styrker og svakheter ved litteratursøk med sortering

Ved litteratursøk gjennomfører vi systematiske søk for en gitt problemstilling. Resultatene fra søket blir i sin helhet overlevert oppdragsgiver, eller vi kan gjennomgå søkeresultatet før overleveringen og sortere ut ikke-relevante artikler. Dette gjøres basert på tittel og sammendrag. Artiklene innhentes ikke i fulltekst. Det gjør at vi kan ha inkludert titler som ville vist seg ikke å være relevante ved gjennomlesning av fulltekst. Vi benytter kun databaser for identifisering av litteratur og kan derfor ha gått glipp av potensielt relevante studier. Andre måter å identifisere studier på, som søk i referanselister, kontakt med eksperter på fagfeltet og upublisert litteratur, er ikke utført i dette oppdraget. Vi gjennomførte ingen kvalitetsvurdering av artiklene.

Ved en full forskningsoppsummering ville vi ha innhentet artiklene/rapportene i fulltekst for endelig vurdering opp mot inklusjonskriteriene. Inkluderte studier ville så blitt kvalitetsvurdert i henhold til våre sjekklister og resultater sammenstilt og diskutert.

Vi har søkt etter allerede gjennomførte oversikter, og fanger dermed ikke opp de nyeste studiene på feltet som er publisert senere enn arbeidet med oversiktene. Vi fanger heller ikke opp studier som omhandler forebygging av allergi, men som av ulike grunner ikke allerede er oppsummert.

Fordelen med å fokusere på oversikter er at man får et innblikk i hva som er gjort på feltet som har vært av interesse for andre forskere å se på virkningen av. En slik oversikt over oversikter gir et godt utgangspunkt for å identifisere hvilket felt man ønsker ytterligere oppsummeringer fra, enten det gjelder effekt av gitte tiltak eller en identifisering av tiltak som er gjennomført for et spesifikt problem. Hvis man alltid skal vurdere enkeltstudier vil det bli et mye større prosjekt som krever mer arbeid for å sammenstille resultatene.

Begrunnelse for valg av søkestrategi

Vi har søkt i elektroniske databaser etter systematiske oversikter. Søket er gjort for tidsperioden fra 2009 fram til juli 2012. Vi har ikke søkt etter grå litteratur eller liknende.

Problemstilling

I prosjektet har vi søkt etter oversikter som skal belyse problemstillinger knyttet til forebygging av allergi hos barn. Vi har ikke søkt kun etter oversikter som omfatter forebygging, men også litteratur som belyser om det er ulike forekomst av allergi i ulike grupper, som vil kunne identifisere faktorer som bør inngå i forebyggingsarbeidet. Selv om bestillingen er knyttet til forebygging har vi også tatt med studier om faktorer som ikke nødvendigvis kan forebygges, som geografiske områder og sykdomsforekomst. Vi tenker allikevel at slik informasjon er interessant for å få en oversikt over hva man vet om det som utløser sykdommen. Studier som berører hva som forverrer sykdommen er ikke tatt med.

Metode

Litteratursøking

Vi søkte systematisk etter litteratur i følgende databaser:

- Medline Ovid(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Cochrane Database of Systematic Reviews
- CRD – DARE og HTA
- PubMed (artikler som er Ahead of print).

Bibliotekar Mariann Mathisen planla og utførte samtlige søk i perioden 31. juli 2012-2. august 2012. De fullstendige søkestrategiene følger vedlagt.

Vi la bestillingen til grunn ved utarbeiding av litteratursøket og søkte etter systematiske oversikter som oppfylte våre inklusjonskriterier for populasjon og intervensjon.

Inklusjonskriterier

Populasjon:	Barn
Tiltak:	Alle faktorer som utløser ulike former for allergi, forebygging av allergi
Sammenlikning:	Ingen eller andre tiltak
Utfall:	Ulike typer allergier
Studiedesign	Systematiske oversikter
Språk:	Ingen begrensninger

Artikkelutvelging

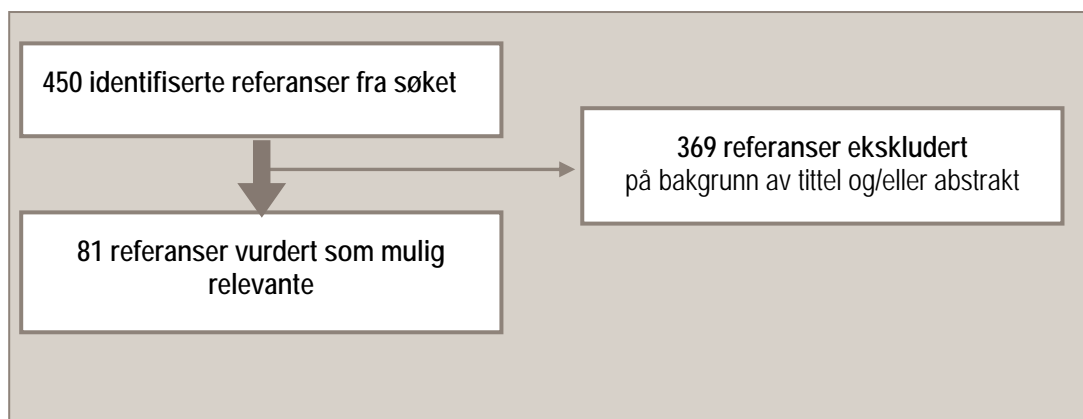
To prosjektmedarbeidere, Hilde H. Holte og Mariann Mathisen, gikk gjennom alle titler og sammendrag for å vurdere relevans i henhold til inklusjonskriteriene. Vurderingene gjorde de uavhengig av hverandre og sammenlignet i etterkant. Der det var uenighet om vurderingene, ble inklusjon eller eksklusjon avgjort ved konsensus.

Utvelging av litteratur ble kun gjort basert på tittel og sammendrag. Vi bestilte ikke fulltekst av artiklene.

Resultat

Resultat av søk

Søket resulterte i 714 referanser. Etter dublettkontroll satt vi igjen med 450 unike referanser. Vi vurderte 81 av de identifiserte referansene til å være mulig relevante i henhold til inklusjonskriteriene.



Figur 1. Flytskjema over identifisert litteratur

Resultat av sorteringen

De mulig relevante referansene ble sortert i 5 kategorier ut fra faktorer som muligens kan utløse ulike typer allergi. Vi identifiserte ingen oversikter som rettet seg mot tiltak som ville forebygge allergi.

Her presenterer vi referansene fordelt i kategoriene og alfabetisk etter førsteforfatter. Vi oppgir forfattere, tittel på publikasjonen og publikasjonssted slik de fremkom i de elektroniske databasene.

Tabell 1: Antall oversikter sortert etter typer faktorer som kan utløse allergi. Ingen identifiserte oversikter om tiltak som kan forebygge allergi.

Tiltak	Antall referanser: 80
Retningslinjer, andre påvirkningsfaktorer, geografiske områder	4
Faktorer knyttet til gener, foreldrenes sykdom eller handlinger	17
Faktorer knyttet til barnets sykdomshistorie	13
Faktorer knyttet til barnets ernæring	25
Faktorer knyttet til barnets omgivelser	22

Nedenfor listes referansene til oversiktene innen hver kategori. Innenfor hver kategori er oversiktene sortert alfabetisk etter førsteforfatter.

Retningslinjer, analyse av andre påvirkende faktorer og betydning av geografisk område.

Oversiktene omfatter en retningslinje, en studie om betydningen av å inkludere andre faktorer som kan påvirke forekomsten av astma og allergi, samt studier om samvariasjon mellom geografisk område og forekomst av astma eller allergi. Oversiktene er sortert alfabetisk etter førsteforfatter.

Katellaris CH, Lee BW, Potter PC, Maspero JF, Cingi C, Lopatin A, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. Clin Exp Allergy 2012;42(2):186-207.

Abstract: BACKGROUND: There is comparatively little information in the public domain on the diversity in prevalence and triggers/factors associated with allergic rhinitis (AR) or allergic rhinoconjunctivitis (AR/C) in countries beyond western-Europe and North America., OBJECTIVE: To review the prevalence and the sensitizing agents/triggers and factors associated with AR/C in several countries in Africa, the Asia-Pacific region, Australia, Eastern Europe, Latin America, Middle East and Turkey., METHODS: Articles published in English in peer-reviewed journals were assessed and selected for further review, following an extensive literature search using the Medline database., RESULTS: This review demonstrated that prevalence of AR and AR/C in these regions has predominantly been investigated in children; with studies indicating wide inter- and intra-regional variations ranging from 2.9% AR and 3.8% AR/C in 10-18-years-old children from one region in Turkey to 54.1% AR and 39.2% AR/C in 13-14-years-old children in one region in Nigeria. Moreover, the prevalence of AR and AR/C has increased markedly over the last decade particularly in some of the more affluent African countries, China-Taiwan and several Middle East countries, likely as a consequence of improved living standards leading to increased exposure to multiple traditional and non-traditional sensitizing agents and risk factors similar to those noted in western-Europe and North

America., CONCLUSIONS AND CLINICAL RELEVANCE: Our findings suggest that the greater diversity in prevalence of AR or AR/C in populations in these regions is in contrast to the lower diversity of AR or AR/C in the 'western populations (USA and Europe), which tend to be more uniform. This review provides a comprehensive database of the important allergens and triggers which are likely to influence the prevalence of allergic rhinitis in these diverse regions, where the prevalence of allergic rhinitis is increasing and its adverse impact on the quality of life of affected individuals is increasingly recognised.

Muche-Borowski C, Kopp M, Reese I, Sitter H, Werfel T, Schafer T, et al. Allergy prevention. J Deutschen Dermatologischen Gesellschaft 2010;8(9):718-24.

Abstract: The further increase of allergies in industrialized countries demands evidence-based measures of primary prevention. The recommendations as published in the guideline of 2004 were updated and consented on the basis of a systematic literature search. Evidence from the period February 2003-May 2008 was searched in the electronic databases Cochrane and MEDLINE as well as in reference lists of recent reviews and by contacting experts. The retrieved citations were screened for relevance first by title and abstract and in a second step as full paper. Levels of evidence were assigned to each included study and the methodological quality of the studies was assessed as high or low. Finally the revised recommendations were formally consented (nominal group process) by representatives of relevant societies and organizations including a self-help group. Of originally 4556 hits, 217 studies (4 Cochrane Reviews, 14 meta-analyses, 19 randomized controlled trials, 135 cohort and 45 case-control studies) were included and critically appraised. Grossly unchanged remained the recommendations on avoiding environmental tobacco smoke, breast-feeding over 4 months (alternatively hypoallergenic formulas for children at risk), avoiding a mold-promoting indoor climate, vaccination according to current recommendations, and avoidance of furry pets (especially cats) in children at risk. The recommendation on reducing the house dust mite allergen exposure as a measure of primary prevention was omitted and the impact of a delayed introduction of supplementary food was reduced. New recommendations were adopted concerning fish consumption (during pregnancy / breast-feeding and as supplementary food in the first year), avoidance of overweight, and reducing the exposure to indoor and outdoor air pollutants. The revision of this guideline on a profound evidence basis led to (1) a confirmation of existing recommendations, (2) substantial revisions, and (3) new recommendations. Thereby it is possible to give evidence-based and up-to-date recommendations on primary prevention of allergies

Nurmatov U, Nwaru BI, Devereux G, Sheikh A. Confounding and effect modification in studies of diet and childhood asthma and allergies. Allergy 2012;67(8):1041-59.

Abstract: OBJECTIVE: To propose a comprehensive set of confounders and effect modifiers that should be considered in epidemiologic investigations., METHODS: Two reviewers independently critiqued studies included in a recent systematic review and extracted data on the confounders and effect modifiers that were considered and the approaches used to justify inclusion., RESULTS: Of the 62 studies reviewed, 20 were cohort, 16 case-control, 25 cross-sectional studies, and one ecologic study. All cohort, cross-sectional, and ecologic studies had some adjustment for confounding or consideration of effect modification, but this was only the case for 7/16 (44%) case-control studies. Of the 53 studies that considered confounding or effect modification, 39/53 (74%) gave no justification for the inclusion of the variables considered. Studies that justified the inclusion of the variables did so based on empirical evidence (n[NON-BREAKING SPACE]=[NON-BREAKING SPACE]10), conceptual justification (n[NON-

BREAKING SPACE]=[NON-BREAKING SPACE]7), or a combination of the two (n[NON-BREAKING SPACE]=[NON-BREAKING SPACE]3). Confounding was handled mainly by using regression modeling, but some case-control studies utilized matching and anova. Ten studies handled effect modification by stratification, eight tested for interaction, and five used both strategies., CONCLUSIONS: We have found substantial shortcomings in the handling of confounding and effect modification in studies of diet and development of childhood asthma/allergies. Selection of variables should be based on conceptual considerations and empirical evidence. Using this approach, we have proposed a comprehensive set of confounders and effect modifiers that need to be considered in future studies.

van Gemert F, van der Molen T, Jones R, Chavannes N. The impact of asthma and COPD in sub-Saharan Africa. Prim care respir j 2011;20(3):240-8.

Abstract: BACKGROUND: Many countries in sub-Saharan Africa have the highest risk of developing chronic diseases and are the least able to cope with them., AIMS: To assess the current knowledge of the prevalence and impact of asthma and chronic obstructive pulmonary disease (COPD) in sub-Saharan Africa., METHODS: A literature search was conducted using Medline (1995-2010) and Google Scholar., RESULTS: Eleven studies of the prevalence of asthma in sub-Saharan Africa were identified, all of which showed a consistent increase, particularly in urban regions. The data on asthma show a wide variation (5.7-20.3%), with the highest prevalence in 'westernised' urban areas. Only two studies of the prevalence of COPD in sub-Saharan Africa have been performed. Nevertheless, COPD has become an increasing health problem in sub-Saharan Africa due to tobacco smoking and exposure to biomass fuels. In most countries of sub-Saharan Africa, 90% of the rural households depend on biomass fuel for cooking and heating, affecting young children (acute lower respiratory infections) and women (COPD). This is the cause of significant mortality and morbidity in the region., CONCLUSIONS: Asthma and COPD in sub-Saharan Africa are under-recognised, under-diagnosed, under-treated, and insufficiently prevented. A major priority is to increase the awareness of asthma and COPD and their risk factors, particularly the damage caused by biomass fuel. Surveys are needed to provide local healthcare workers with the possibility of controlling asthma and COPD

Genetiske faktorer og påvirkning fra foreldrenes sykdom eller handlinger

Studiene omfatter betydningen av gener, av rekkefølgen i søskenflokk, av mors ernæring og bruk av medisiner, og psykologiske faktorer. Oversiktene er sortert alfabetisk etter førsteforfatter.

Cui L, Jia J, Ma CF, Li SY, Wang YP, Guo XM, et al. IL-13 polymorphisms contribute to the risk of asthma: a meta-analysis. Clin Biochem 2012;45(4-5):285-8.

Abstract: OBJECTIVES: The purpose of this study was to evaluate the effects of interleukin-13 (IL-13) polymorphisms on the risk of asthma using a meta-analysis., DESIGN AND METHODS: Fifteen publications were identified by searching Pubmed, Embase, ISI, OVID, and EBSCO databases. Odds ratios with corresponding 95% confidence intervals were computed to estimate the association between IL-13 polymorphisms and risk of asthma., RESULTS: The polymorphisms of R130Q (rs20541) and -1112C/T (rs1800925) in IL-13 gene were associated with significantly increased risks of asthma in overall analyses. Sub-

group analyses showed that the elevated risks occurred in adult-onset asthma, Caucasians, and high quality studies., CONCLUSIONS: This meta-analysis provides evidence that the R130Q and -1112C/T polymorphisms in IL-13 are risk factors for asthma.

Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. Clin Exp Allergy 2011;41(4):482-9.

Abstract: BACKGROUND: There is evidence to suggest that the risk of asthma might be increased with exposure to paracetamol in the intrauterine environment, infancy, later childhood and adult life., OBJECTIVE: To review the evidence from studies investigating the association between paracetamol use in pregnancy and childhood asthma., METHODS: A systematic review and meta-analysis was undertaken of studies reporting the association between paracetamol use in pregnancy and subsequent asthma in childhood. The primary outcome variable was wheeze in the last 12 months. For tabulated raw data, not adjusted for confounders, random effects odds ratios (OR) were pooled by the inverse variance weighted method., RESULTS: There were six studies identified that were included in the meta-analysis. The age of children studied ranged from 30 to 84 months. The pooled random effects OR for the risk of current wheeze in the children of women who were exposed to any paracetamol during any stage of pregnancy was 1.21 (95% confidence interval 1.02-1.44). Features of the studies variably included an association with paracetamol use during all trimesters of pregnancy and an association with persistent asthma, severe asthma, and with atopy., CONCLUSION AND CLINICAL RELEVANCE: The use of paracetamol during pregnancy is associated with an increased risk of childhood asthma. More research is urgently required to determine the impact of paracetamol during pregnancy on the risk of wheezing in offspring so that appropriate public health recommendations can be made.

Jurewicz J, Hanke W. Exposure to phthalates: reproductive outcome and children health. A review of epidemiological studies. Int J Occup Med Environ Health 2011;24(2):115-41.

Abstract: Phthalates are a family of industrial chemicals that have been used for a variety of purposes. As the potential consequences of human exposure to phthalates have raised concerns in the general population, they have been studied in susceptible subjects such as pregnant women, infants and children. This article aims at evaluating the impact of exposure to phthalates on reproductive outcomes and children health by reviewing most recent published literature. Epidemiological studies focusing on exposure to phthalates and pregnancy outcome, genital development, semen quality, precocious puberty, thyroid function, respiratory symptoms and neurodevelopment in children for the last ten years were identified by a search of the PubMed, Medline, Ebsco, Agricola and Toxnet literature bases. The results from the presented studies suggest that there are strong and rather consistent indications that phthalates increase the risk of allergy and asthma and have an adverse impact on children's neurodevelopment reflected by quality of alertness among girls, decreased (less masculine) composite score in boys and attention deficit hyperactivity disorder. Results of few studies demonstrate negative associations between phthalate levels commonly experienced by the public and impaired sperm quality (concentration, morphology, motility). Phthalates negatively impact also on gestational age and head circumference; however, the results of the studies were not consistent. In all the reviewed studies, exposure to phthalates adversely affected the level of reproductive hormones (luteinizing hormone, free testosterone, sex hormone-binding globulin), anogenital distance and thyroid function. The urinary levels of phthalates were significantly higher in the pubertal gynecomastia group, in serum in girls with premature thelarche and in girls with precocious puberty. Epidemiological studies, in spite of their limitations, suggest that phthalates may affect repro-

ductive outcome and children health. Considering the suggested health effects, more epidemiologic data is urgently needed and, in the meantime, precautionary policies must be implemented

Klemens CM, Berman DR, Mozurkewich EL. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: a systematic review. *BJOG* 2011;118(8):916-25.

Abstract: BACKGROUND: Maternal supplementation with omega-3 polyunsaturated fatty acids (n-3 PUFA) may modulate immune responses and allergy in neonates and children., OBJECTIVE: To determine if n-3 PUFA supplementation during pregnancy and lactation reduces risk for childhood allergic disease., SEARCH STRATEGY: We searched Medline and all evidence-based medicine reviews for randomised controlled trials comparing the effects of n-3 PUFA and placebo supplementation during pregnancy and/or lactation on childhood allergic diseases and inflammatory cytokines., SELECTION CRITERIA: We included studies reporting on food allergy, response to the egg skin prick test (SPT), atopy and asthma in infancy and childhood as well as production of interleukin-13 and interferon-gamma, two cytokines involved in the pathogenesis of asthma. For assessment of inclusion, two authors reviewed all abstracts for suitability and independently extracted data., DATA COLLECTION AND ANALYSIS: Two-by-two tables were constructed and odds ratios (OR) were calculated for the outcomes: response to the SPT, food allergy, atopy and asthma in childhood. The assays differed so data on inflammatory markers were reported in narrative form., MAIN RESULTS: Five randomised controlled trials (n = 949) were included. n-3 PUFA supplementation during pregnancy reduced 12-month prevalence of positive egg SPT (two trials, 12/87 versus 32/100, OR 0.33, 95% CI 0.16, 0.70) and childhood asthma (two trials, 10/303 versus 17/179, OR 0.349, 95% CI 0.154, 0.788) and significantly reduced cord blood interleukin-13 levels. Supplementation during lactation did not prevent asthma, food allergy or atopy., CONCLUSION: n-3 PUFA supplementation during pregnancy decreases childhood asthma and response to SPT.

Kruse LV, Nyegaard M, Christensen U, Moller-Larsen S, Haagerup A, Deleuran M, et al. A genome-wide search for linkage to allergic rhinitis in Danish sib-pair families. *European journal of human genetics : EJHG* 2012; Mar 14. doi: 10.1038/ejhg.2012.46. [Epub ahead of print]

Abstract: Allergic rhinitis (AR) is a complex disorder with a polygenic, multifactorial aetiology. Twin studies have found the genetic contribution to be substantial. We collected and clinically characterised a sample consisting of 127 Danish nuclear families with at least two siblings suffering from AR or allergic conjunctivitis including 540 individuals (286 children and 254 parents). A whole-genome linkage scan, using 424 microsatellite markers, was performed on both this sample and an earlier collected sample consisting of 130 families with atopic dermatitis and other atopic disorders. A third sib-pair family sample, which was previously collected and genotyped, was added to the analysis increasing the total sample size to 357 families consisting of 1508 individuals. In total, 190 families with AR was included. The linkage analysis software Genehunter NPL, Genehunter MOD, and Genehunter Imprinting were used to obtain nonparametric and parametric linkage results. Family-based association analysis of positional candidate SNPs was carried out using the FBAT program. We obtained genome-wide significant linkage to a novel AR locus at 1p13 and suggestive linkage to two novel regions at 1q31-q32 and 20p12, respectively. Family-based association analysis of SNPs in the candidate locus DNND1B/CRB1 at 1q31 showed no significant association and could not explain the linkage signal observed. Suggestive evidence of linkage was also obtained at three AR loci previously reported (2q14-q23, 2q23, and 12p13) and indication of linkage was observed at a number of addi-

tional loci. Likely maternal imprinting was observed at 2q23, and possible maternal imprinting at 3q28.

Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. PloS one 2010;5(4):e10134.

Abstract: BACKGROUND: Many human epidemiologic studies demonstrate that maternal asthma confers greater risk of asthma to offspring than does paternal disease. However, a handful have shown the opposite. Given this disparity, a meta-analysis is necessary to determine the veracity and magnitude of the "maternal effect.", METHODOLOGY/PRINCIPAL FINDINGS: We screened the medical literature from 1966 to 2009 and performed a meta-analysis to compare the effect of maternal asthma vs. paternal asthma on offspring asthma susceptibility. Aggregating data from 33 studies, the odds ratio for asthma in children of asthmatic mothers compared with non-asthmatic mothers was significantly increased at 3.04 (95% confidence interval: 2.59-3.56). The corresponding odds ratio for asthma in children of asthmatic fathers was increased at 2.44 (2.14-2.79). When comparing the odds ratios, maternal asthma conferred greater risk of disease than did paternal asthma (3.04 vs. 2.44, $p = 0.037$). When analyzing the studies in which asthma was diagnosed by a physician the odds ratios were attenuated and no significant differences were observed (2.85 vs. 2.48, $N = 18$, $p = 0.37$). Similarly, no significant differences were observed between maternal and paternal odds ratios when analyzing the studies in which the patient population was 5 years or older (3.15 vs. 2.60, $p = 0.14$). However, in all cases the trend remained the same, that maternal asthma was a greater risk factor for asthma than paternal., CONCLUSIONS/SIGNIFICANCE: The results show that maternal asthma increases offspring disease risk to a greater extent than paternal disease.

Patelarou E, Giourgouli G, Lykeridou A, Vrioni E, Fotos N, Siamaga E, et al. Association between biomarker-quantified antioxidant status during pregnancy and infancy and allergic disease during early childhood: a systematic review. Nutr Rev 2011;69(11):627-41.

Abstract: Recent findings suggest a significant association between the antioxidant status of pregnant women and of their children during the first years of life and the development of allergic disease during childhood. The aim of this review was to identify all studies that estimated the effect of intake of antioxidants in pregnant women and their children on the development of allergic disease during early childhood. A systematic review was conducted of epidemiological studies featuring original peer-reviewed data on the association between dietary antioxidant status and allergic disease during childhood. A systematic search was performed following the Meta-analysis of Observational Studies in Epidemiology Guidelines. A comprehensive search of the literature yielded 225 studies, 18 of which were selected for the extraction of results and were related to antioxidant status and allergic disease. The systematic review included five prospective cohort studies, four cross-sectional studies, and nine case-control studies. Eight studies reported an important association between antioxidant status and asthma onset during childhood. Similarly, wheezing and eczema were studied as an outcome in six and in five studies, respectively. Recent observational studies suggest that a higher intake of antioxidant vitamins, zinc, and selenium during pregnancy and childhood reduces the likelihood of childhood asthma, wheezing, and eczema.

Ricci G, Astolfi A, Remondini D, Cipriani F, Formica S, Dondi A, et al. Pooled genome-wide analysis to identify novel risk loci for pediatric allergic asthma. PloS one 2011;6(2):e16912.

Abstract: BACKGROUND: Genome-wide association studies of pooled DNA samples were shown to be a valuable tool to identify candidate SNPs associated to a phenotype. No such study was up to now applied to childhood allergic asthma, even if the very high complexity of asthma genetics is an appropriate field to explore the potential of pooled GWAS approach., METHODOLOGY/PRINCIPAL FINDINGS: We performed a pooled GWAS and individual genotyping in 269 children with allergic respiratory diseases comparing allergic children with and without asthma. We used a modular approach to identify the most significant loci associated with asthma by combining silhouette statistics and physical distance method with cluster-adapted thresholding. We found 97% concordance between pooled GWAS and individual genotyping, with 36 out of 37 top-scoring SNPs significant at individual genotyping level. The most significant SNP is located inside the coding sequence of C5, an already identified asthma susceptibility gene, while the other loci regulate functions that are relevant to bronchial physiopathology, as immune- or inflammation-mediated mechanisms and airway smooth muscle contraction. Integration with gene expression data showed that almost half of the putative susceptibility genes are differentially expressed in experimental asthma mouse models., CONCLUSION/SIGNIFICANCE: Combined silhouette statistics and cluster-adapted physical distance threshold analysis of pooled GWAS data is an efficient method to identify candidate SNP associated to asthma development in an allergic pediatric population

Shams K, Grindlay DJC, Williams HC. What's new in atopic eczema? An analysis of systematic reviews published in 2009-2010. Clin Exp Dermatol 2011;36(6):573-8.

Abstract: This review provides a summary of key findings from 18 systematic reviews on atopic eczema, published or indexed between January 2009 and 24 August 2010. There was no good evidence on the possible benefit of organic food consumption and eczema. Maternal intake of fish or fish oil may be associated with a reduced risk of eczema in offspring, although further studies are needed. There is some evidence that partially hydrolysed infant formulas rather than standard formulas may be associated with a reduced risk of eczema in infants, but there are shortcomings in the existing evidence. An inverse relationship has been found between gliomas/acute lymphoblastic leukaemia and allergic disease/eczema, but there appears to be no association between multiple sclerosis and eczema. Attention deficit hyperactivity disorder does appear to be associated with eczema, but there is no evidence of a causal link. The risk of eczema seems to be increased in urban compared with rural areas. Some new evidence has suggested superiority of 1% pimecrolimus over potent and mild corticosteroids at 6[em space]months but not 12[em space]months, and there is some evidence for superiority of 0.03% and 0.1% tacrolimus over 1% pimecrolimus. An updated Cochrane Review still found no evidence of a benefit from any form of antistaphylococcal treatment in managing clinically infected or uninfected eczema. The evidence base is poor for bath emollients, occlusive treatments (e.g., wet and dry wraps) and woven silk clothing in treating eczema. In general, the methods used in most systematic reviews of eczema need to be reported more clearly, especially with regard to a more vigorous quality assessment of included studies. Included studies are frequently heterogeneous, proxy reporting is common, and appropriate disease definitions are often lacking. Better adherence to existing guidance on trial reporting and prospective registration of clinical trials may help improve the quality of studies.

Tibosch MM, Verhaak CM, Merkus PJFM. Psychological characteristics associated with the onset and course of asthma in children and adolescents: a systematic review of longitudinal effects. Patient Educ Couns 2011;82(1):11-9.

Abstract: OBJECTIVE: to systematically review all available studies that investigated the longitudinal relationships between the psychological characteristics of children and adolescents suffering from asthma and those of their caregivers, and the onset and course of the asthma., METHODS: relevant studies were identified using Medline, PubMed, and PsychINFO between 1970 and September 2009., RESULTS: twenty studies matching inclusion criteria were reviewed. Six studies focused on child-specific psychological characteristics in relation to the onset and course of asthma. No compelling evidence was found for an association with asthma onset, but there was some evidence that the child's psychological characteristics can contribute to the subsequent course of asthma. Fourteen studies considered the effects of the psychological characteristics of the caregivers. Eleven studies found significant relationships between the psychological problems of caregivers and the subsequent onset and unfavorable course of the asthma in the child., CONCLUSION: in pediatric asthma both the psychological characteristics of the affected children and their caregivers appear to contribute to the course and possibly also to the onset of the condition.

Upchurch S, Harris JM, Cullinan P. Temporal changes in UK birth order and the prevalence of atopy. Allergy 2010;65(8):1039-41.

Abstract: BACKGROUND: Many studies have reported an inverse association between birth order and the risk of respiratory allergic disease. In recent decades, the prevalence of atopy has increased alongside reductions in fertility rates., AIMS OF THE STUDY: To quantitate how much of the increased prevalence of atopy, measured by skin prick test or specific IgE, can be attributed to temporal changes in family size in the United Kingdom., METHODS: Through a systematic literature review (MEDLINE, 1965-2009), five studies of UK populations were identified and their data were included in the calculation of a summary odds ratio for the risk of atopy for each birth order. Information on changes in UK family sizes between 1960 and 2001 was obtained from Eurostat. On this basis, expected increases in the prevalence of atopy were calculated by weighting the proportion in each birth order category for 1960 and 2001 by the summary odds ratio for that category and then calculating the relative risk of atopy in 2001 compared with 1960., RESULTS: The pooled summary odds ratios for atopy were 0.90, 0.69 and 0.69 for those born second, third and fourth (or higher), respectively. The expected relative increase in the prevalence of atopy resulting from a change in family size between 1960 and 2001 was 3%., CONCLUSIONS: Despite the strong associations between birth order and atopy, reductions in family size in the last 40 years account for little of the increase in atopy

Williams HC, Grindlay DJC. What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008. Part 2. Disease prevention and treatment. Clin Exp Dermatol 2010;35(3):223-7.

Abstract: This review summarizes clinically important findings from systematic reviews indexed in bibliographical databases between August 2007 and August 2008 that dealt with disease prevention (six reviews) and treatment of atopic eczema (seven reviews). Regarding disease prevention, two independent systematic reviews found some clinical trial evidence that ingestion of probiotics by mothers during pregnancy might reduce the incidence of subsequent eczema. Another review failed to find any clear benefit of prebiotics in eczema prevention. Although furry pets are often cited as caus-

ing allergic disease, a systematic review of observational studies found no evidence that exposure to cats or dogs at birth increases eczema risk. One very large review of studies of breastfeeding found some evidence of a protective effect on eczema risk, although all the studies were limited by their observational nature. A German group has attempted an overview of eczema prevention studies with a view to informing national guidelines. In terms of eczema treatment, two systematic reviews have confirmed the efficacy of topical tacrolimus ointment. Another review of 31 trials confirms the efficacy of topical pimecrolimus, although many of those trials were vehicle controlled, which limits their clinical utility. A review of 23 studies of desensitization therapy for allergic diseases found some evidence of benefit for eczema, which needs to be explored further. Despite the popularity of antistaphylococcal therapies for eczema, a Cochrane Review of 21 trials failed to show any clear benefit for any of the therapies for infected or clinically noninfected eczema. Another Cochrane Review dealt with dietary exclusions for people with eczema and found little evidence to support any dietary exclusion, apart from avoidance of eggs in infants with suspected egg allergy supported by evidence of sensitization. A review of 13 studies of probiotics for treating established eczema did not show convincing evidence of a clinically worthwhile benefit, an observation that has been substantiated in a subsequent Cochrane Review

Wu H, Romieu I, Sienra-Monge JJ, Li H, del Rio-Navarro BE, London SJ. Genetic variation in ORM1-like 3 (ORMDL3) and gasdermin-like (GSDML) and childhood asthma. *Allergy* 2009;64(4):629-35.

Abstract: BACKGROUND: A genome-wide association study identified ORM1-like 3 (orosomucoid 1-like 3, ORMDL3) as an asthma candidate gene. Single nucleotide polymorphisms (SNPs) in the region including ORMDL3 on chromosome 17q21 were related to childhood asthma risk and ORMDL3 expression levels in Europeans., OBJECTIVE: We examined whether polymorphisms in ORMDL3 and the adjacent gasdermin-like (GSDML) gene associated with asthma in the genome-wide association study are related to childhood asthma and atopy in a Mexico City population., METHODS: We genotyped rs4378650 in ORMDL3 and rs7216389 in GSDML in 615 nuclear families consisting of asthmatic children aged 4-17 years and their parents. Atopy was determined by skin prick tests to 25 aeroallergens., RESULTS: Individuals carrying the C allele of rs4378650 or the T allele of rs7216389 had increased risk of asthma [relative risk (RR) = 1.73, 95% confidence interval (CI) 1.19-2.53, P = 0.003 for one or two copies of rs4378650 C, and RR = 1.64, 95% CI 1.12-2.38, P = 0.009 for one or two copies of rs7216389 T]. Linkage disequilibrium between the two SNPs was high ($r(2) = 0.92$). Neither of the SNPs was associated with the degree of atopy. A meta-analysis of five published studies on rs7216389 in nine populations gave an odds ratio for asthma of 1.44 (95% CI, 1.35-1.54, P < 0.00001)., CONCLUSIONS: Our results and the meta-analysis provide evidence to confirm the finding from a recent genome-wide association study that polymorphisms in ORMDL3 and the adjacent GSDML may contribute to childhood asthma

Zhang YG, Huang J, Zhang J, Li XB, He C, Xiao YL, et al. RANTES gene polymorphisms and asthma risk: A meta-analysis. *Arch Med Res* 2010;41(1):50-8.

Abstract: BACKGROUND AND AIMS: RANTES is a chemokine that assists the recruitment of inflammatory cells including eosinophils. Previous studies revealed that polymorphisms of RANTES were implicated in susceptibility to asthma, but a large number of studies reported apparently conflicting results. We performed a meta-analysis to investigate the association of these polymorphisms and asthma risk., METHODS: Literature-based meta-analysis was supplemented by tabular data from investigation of all

relevant studies regarding all polymorphisms of RANTES available before November 30, 2009, with investigation on potential sources of heterogeneity., RESULTS: Ten case/control studies were included in the meta-analysis, involving a total of 1706 cases and 1685 controls. In a combined analysis, no significant associations with asthma risk were found on these two polymorphisms (-403G/A and -28C/G) without any publication bias. For the -403G/A polymorphism, in subgroup analysis by ethnicity, no significant associations were found in Asians, Europeans or African-Americans; in subgroup analysis by age, no significant associations were found in adults or children. In subgroup analysis by atopic status, the -403G/A polymorphism was significantly associated with asthma risk in atopic asthma (dominant model [OR = 1.38, 95% CI = 1.09-1.76, p = 0.009; P(het) = 0.10]; A vs. G model [OR = 1.25, 95% CI = 1.04-1.51, p = 0.02; P(het) = 0.11] and AG vs. GG model [OR = 1.37, 95% CI = 1.06-1.77, p = 0.02; P(het) = 0.14])., CONCLUSIONS: This meta-analysis suggested that RANTES gene -403G/A polymorphism would be a risk factor among atopic asthma patients. To further evaluate gene-to-gene and gene-to-environment interactions on RANTES polymorphisms and asthma risk, more studies with thousands of patients are required.

Zhang Y, Zhang J, Huang J, Li X, He C, Tian C, et al. Polymorphisms in the transforming growth factor-beta1 gene and the risk of asthma: A meta-analysis. *Respirology* 2010;15(4):643-50.

Abstract: BACKGROUND AND OBJECTIVE: Polymorphisms in the transforming growth factor-beta1 (TGF-beta1) gene have been implicated in susceptibility to asthma, but a large number of studies have reported inconclusive results. A meta-analysis was performed to investigate the association between polymorphisms in the TGF-beta1 gene and asthma susceptibility., METHODS: Searches were performed of Medline (Ovid), PubMed, the Chinese Biological Medicine Database (CBM), the Chinese Journals Full-text Database (CNKI), the Cochrane Library Database and the Web of Science, covering all papers published up to 30 April 2009. Statistical analysis was performed using Revman4.2.8 and STATA10.0 software., RESULTS: Two polymorphisms (-509C/T and 915G/C(G25C)) were investigated in 14 studies, involving 2979 asthma patients and 4941 control subjects. The results showed that individuals carrying the -509T allele (TT+TC) had a 36% increased risk of asthma, when compared with homozygotes (-509CC) (OR 1.36, 95% CI: 1.12-1.65). However, there was no significant association with risk of asthma in carriers of the 915C allele (GC+CC) compared with 915GG homozygotes (OR 1.05, 95% CI: 0.65-1.70). In a subgroup analysis by ethnicity, the risk of asthma associated with the -509T allele was significantly elevated among Asians (OR 1.50, 95% CI: 1.04-2.17) but not Caucasians (OR 1.16, 95% CI: 1.00-1.36). In a subgroup analysis by age, the -509T allele was associated with a significantly elevated risk of asthma among adults (OR 1.45, 95% CI: 1.09-1.92) but not children (OR 1.19, 95% CI: 0.96-1.46)., CONCLUSIONS: This meta-analysis suggested that the -509C/T polymorphism in the TGF-beta1 gene may be a risk factor for asthma. To further evaluate gene-gene and gene-environment interactions between polymorphisms in the TGF-beta1 gene and asthma susceptibility, more studies involving thousands of patients are required

Zhang Y, Tian C, Zhang J, Li X, Wan H, He C, et al. The -159C/T polymorphism in the CD14 gene and the risk of asthma: a meta-analysis. *Immunogenetics* 2011;63(1):23-32.

Abstract: BACKGROUND: The -308 G/A polymorphism in TNF-alpha gene has been extensively investigated for association to asthma; however, results of different studies have been inconsistent. The aim of this study is to comprehensively evaluate the genetic risk of -308 G/A polymorphism in TNF-alpha gene for asthma., METHODS: A meta-analysis was carried out to analyze the association between the -308 G/A polymor-

phism TNF-alpha gene and asthma risk., RESULTS: A total of 4717 cases and 5012 controls in 29 case-control studies were included in this meta-analysis. The result indicated that the variant A allele carriers had a 38% increased risk of asthma, when compared with the homozygote GG (odds ratio (OR)[THIN SPACE]=[THIN SPACE]1.40, 95% confidence interval (CI), 1.13-1.68 for AA[THIN SPACE]+[THIN SPACE]AG vs. GG). In the subgroup analysis by ethnicity, significant elevated risks were associated with A allele carriers in Asians (OR[THIN SPACE]=[THIN SPACE]1.53, 95% CI[THIN SPACE]=[THIN SPACE]1.17-2.01 and P[THIN SPACE]=[THIN SPACE]0.002) but not in Caucasians(OR[THIN SPACE]=[THIN SPACE]1.06, 95% CI[THIN SPACE]=[THIN SPACE]0.75-1.50 and P[THIN SPACE]=[THIN SPACE]0.73). In the subgroup analysis by age, significant elevated risks were associated with A allele carriers in adults (OR[THIN SPACE]=[THIN SPACE]1.44, 95% CI[THIN SPACE]=[THIN SPACE]1.14-1.81, and P[THIN SPACE]=[THIN SPACE]0.002) and children (OR[THIN SPACE]=[THIN SPACE]1.37, 95% CI[THIN SPACE]=[THIN SPACE]1.03-1.82, and P[THIN SPACE]=[THIN SPACE]0.003). In the subgroup analysis by atopic status, significant elevated risks of asthma were associated with A allele carriers in atopic population (OR[THIN SPACE]=[THIN SPACE]1.68, 95% CI[THIN SPACE]=[THIN SPACE]1.34-2.10, and P[THIN SPACE]<[THIN SPACE]0.00001) but not in non-atopic population (OR[THIN SPACE]=[THIN SPACE]0.98, 95% CI[THIN SPACE]=[THIN SPACE]0.58-1.68, and P[THIN SPACE]=[THIN SPACE]0.95)., CONCLUSIONS: Our results suggest that the TNF-alpha -308 G/A polymorphism contributes to susceptibility to asthma

Zhang Y, Zhang J, Tian C, Xiao Y, He C, Li X, et al. The -308 G/A polymorphism in TNF-alpha gene is associated with asthma risk: an update by meta-analysis. J Clin Immunol 2011;31(2):174-85.

Abstract: The -159C/T polymorphism in the CD14 gene has been implicated in susceptibility to asthma, but a large number of studies have reported inconclusive results. The aim of this study is to investigate the association between the -159C/T polymorphism in the CD14 gene and the risk of asthma by meta-analysis. We searched Pubmed, Embase, CNKI database, Wanfang database, Weipu database, and Chinese Biomedical database, covering all publications (last search been performed on April 20, 2010). Statistical analysis was performed by using the softwares Revman 4.2 and STATA 10.0. A total of 17 case-control studies in 17 articles (4,246 cases and 3,631 controls) were included in this meta-analysis. There was no association between this polymorphism and asthma risk in combined analyses (odds ratio (OR)[THIN SPACE]=[THIN SPACE]0.86 and 95% confidence interval (95% CI)[THIN SPACE]=[THIN SPACE]0.72-1.02, P[THIN SPACE]=[THIN SPACE]0.09 for TC[THIN SPACE]+[THIN SPACE]TT vs. CC). In the subgroup analysis by age, ethnicity, and atopic status, no significant associations of asthma risks were obtained from age groups, ethnic groups, and atopic groups for TC[THIN SPACE]+[THIN SPACE]TT vs. CC comparison. For atopic population, significant decreased atopic asthma risks were found among Asian population (OR[THIN SPACE]=[THIN SPACE]0.69, 95% CI 0.52-0.92, P[THIN SPACE]=[THIN SPACE]0.01) and children population (OR[THIN SPACE]=[THIN SPACE]0.69, 95% CI 0.54-0.89, P[THIN SPACE]=[THIN SPACE]0.0004) for TC[THIN SPACE]+[THIN SPACE]TT vs. CC comparison. This meta-analysis suggests that CD14 is a candidate gene for atopic asthma susceptibility. The -159C/T polymorphism may be a protective factor for atopic asthma in Asian and children. More studies are needed to validate these associations

Faktorer knyttet til barnets sykdomshistorie.

Studiene omfatter faktorer som er knyttet til barnets sykdomshistorie som at barnet har hatt lungebetennelse eller har fått en fødselsskade, til behandling som vaksiner og bruk av antibiotika. Oversiktene er sortert alfabetisk etter førsteforfatter.

Arnoldussen DL, Linehan M, Sheikh A. BCG vaccination and allergy: a systematic review and meta-analysis. J Allergy Clin Immunol 2011;127(1):246-21.

Abstract: BACKGROUND: There is conflicting evidence on whether BCG vaccination might represent an effective primary preventative strategy against the development of allergic sensitization and disease., OBJECTIVES: We sought to systematically review the relationship between BCG vaccination and the risk of sensitization, eczema/atopic dermatitis, allergic rhinoconjunctivitis, asthma, and other allergic conditions, such as food allergy and anaphylaxis., METHODS: Four international databases were searched for published epidemiologic or interventional studies. Additional online study databases were searched and vaccine manufacturers and a panel of international experts were contacted in an attempt to locate unpublished or ongoing studies. Quality assessment was undertaken by using internationally established criteria. Meta-analyses were undertaken by using fixed- or random-effects modeling. Funnel plots were used to assess for the risk of publication bias., RESULTS: We identified 767 articles, of which 17 satisfied our inclusion criteria; there was only 1 randomized controlled trial, with the remaining studies being epidemiologic investigations. Meta-analyses did not show any protective effect of vaccination against the risk of sensitization, as judged by specific IgE tests (odds ratio [OR], 1.31; 95% CI, 1.07-1.60) or skin prick testing (OR, 0.87; 95% CI, 0.67-1.13); the risk of atopic eczema/dermatitis (OR, 0.84; 95% CI, 0.64-1.09); or the risk of allergic rhinoconjunctivitis (OR, 1.07; 95% CI, 0.89-1.28). BCG vaccination was associated with a protective effect against the risk of asthma (OR, 0.73; 95% CI, 0.56-0.95), although this might be explained by publication bias., CONCLUSIONS: BCG vaccination is unlikely to be associated with protection against the risk of allergic sensitization and disease. The observed possible benefit in relation to the development of asthma is unlikely to be due to allergic sensitization.

Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev 2012;2:CD004407.

Abstract: BACKGROUND: Mumps, measles and rubella (MMR) are serious diseases that can lead to potentially fatal illness, disability and death. However, public debate over the safety of the trivalent MMR vaccine and the resultant drop in vaccination coverage in several countries persists, despite its almost universal use and accepted effectiveness., OBJECTIVES: To assess the effectiveness and adverse effects associated with the MMR vaccine in children up to 15 years of age., SEARCH METHODS: For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 2), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, PubMed (July 2004 to May week 2, 2011) and Embase.com (July 2004 to May 2011)., SELECTION CRITERIA: We used comparative prospective or retrospective trials assessing the effects of the MMR vaccine compared to placebo, do nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age., DATA COLLECTION AND ANALYSIS: Two review authors independently extracted data and assessed methodological quality of the included studies. One review author arbitrated in case of disagreement., MAIN RESULTS: We included five randomised controlled trials (RCTs), one controlled clinical

trial (CCT), 27 cohort studies, 17 case-control studies, five time-series trials, one case cross-over trial, two ecological studies, six self controlled case series studies involving in all about 14,700,000 children and assessing effectiveness and safety of MMR vaccine. Based on the available evidence, one MMR vaccine dose is at least 95% effective in preventing clinical measles and 92% effective in preventing secondary cases among household contacts. Effectiveness of at least one dose of MMR in preventing clinical mumps in children is estimated to be between 69% and 81% for the vaccine prepared with Jeryl Lynn mumps strain and between 70% and 75% for the vaccine containing the Urabe strain. Vaccination with MMR containing the Urabe strain has demonstrated to be 73% effective in preventing secondary mumps cases. Effectiveness of Jeryl Lynn containing MMR in preventing laboratory-confirmed mumps cases in children and adolescents was estimated to be between 64% to 66% for one dose and 83% to 88% for two vaccine doses. We did not identify any studies assessing the effectiveness of MMR in preventing rubella. The highest risk of association with aseptic meningitis was observed within the third week after immunisation with Urabe-containing MMR (risk ratio (RR) 14.28; 95% confidence interval (CI) from 7.93 to 25.71) and within the third (RR 22.5; 95% CI 11.8 to 42.9) or fifth (RR 15.6; 95% CI 10.3 to 24.2) weeks after immunisation with the vaccine prepared with the Leningrad-Zagreb strain. A significant risk of association with febrile seizures and MMR exposure during the two previous weeks (RR 1.10; 95% CI 1.05 to 1.15) was assessed in one large person-time cohort study involving 537,171 children aged between three months and five year of age. Increased risk of febrile seizure has also been observed in children aged between 12 to 23 months (relative incidence (RI) 4.09; 95% CI 3.1 to 5.33) and children aged 12 to 35 months (RI 5.68; 95% CI 2.31 to 13.97) within six to 11 days after exposure to MMR vaccine. An increased risk of thrombocytopenic purpura within six weeks after MMR immunisation in children aged 12 to 23 months was assessed in one case-control study (RR 6.3; 95% CI 1.3 to 30.1) and in one small self controlled case series (incidence rate ratio (IRR) 5.38; 95% CI 2.72 to 10.62). Increased risk of thrombocytopenic purpura within six weeks after MMR exposure was also assessed in one other case-control study involving 2311 children and adolescents between one month and 18 years (odds ratio (OR) 2.4; 95% CI 1.2 to 4.7). Exposure to the MMR vaccine was unlikely to be associated with autism, asthma, leukaemia, hay fever, type 1 diabetes, gait disturbance, Crohn's disease, demyelinating diseases, bacterial or viral infections., AUTHORS' CONCLUSIONS: The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with the MMR vaccine cannot be separated from its role in preventing the target diseases

Dewachter P, Mouton-Faivre C. [[Allergic risk during paediatric anaesthesia](#)]. *Ann Fr Anesth Reanim* 2010;29(3):215-26.

Abstract: OBJECTIVES: To propose the different modalities of management of the allergic risk occurring during paediatric anaesthesia., STUDY DESIGN: Literature analysis., METHODS: Literature research using the Medline((R)) database and MeSH format according to keywords, including publications in French and English since 1982., RESULTS: The overall incidence for anaphylactic reactions was estimated at one in 7741 anaesthetic procedures during paediatric anaesthesia. Latex anaphylaxis was mostly involved with an incidence at one in 10,159 anesthetic procedures. The risk factors of latex sensitization are known. Primary latex prophylaxis is efficient in patients at risk of latex sensitization. In contrast to adults, neuromuscular blocking agents (NMBAs) are rarely involved in children, with an incidence at 1 in 81,275 anaesthetic procedures. The Ring and Messmer clinical scale allows quantifying the severity and helps managing the care of immediate hypersensitivity reactions. Clinical symptoms associate cardiovascular, respiratory and cutaneous-mucous signs according to different severity grades. Epinephrine associated to fluid loading, remains the first-line agent in case of

severe reactions. The allergological assessment is key to the management of these reactions and is required in order to identify the mechanism of the reaction and the culprit drug or substance involved., CONCLUSIONS: Allergic reactions to NMBAs occurring during paediatric anaesthesia are rare whereas those with latex are more frequent. Therefore, the reduction of the allergic risk during paediatric anaesthesia essentially requires a latex-free environment.

Edmond K, Scott S, Korczak V, Ward C, Sanderson C, Theodoratou E, et al. Long term sequelae from childhood pneumonia: systematic review and meta-analysis. PloS one 2012;7(2):e31239.

Abstract: BACKGROUND: The risks of long term sequelae from childhood pneumonia have not been systematically assessed. The aims of this study were to: (i) estimate the risks of respiratory sequelae after pneumonia in children under five years; (ii) estimate the distribution of the different types of respiratory sequelae; and (iii) compare sequelae risk by hospitalisation status and pathogen., METHODS: We systematically reviewed published papers from 1970 to 2011. Standard global burden of disease categories (restrictive lung disease, obstructive lung disease, bronchiectasis) were labelled as major sequelae. 'Minor' sequelae (chronic bronchitis, asthma, other abnormal pulmonary function, other respiratory disease), and multiple impairments were also included. Thirteen papers were selected for inclusion. Synthesis was by random effects meta-analysis and meta-regression., RESULTS: Risk of at least one major sequelae was 5.5% (95% confidence interval [95% CI] 2.8-8.3%) in non hospitalised children and 13.6% [6.2-21.1%]) in hospitalised children. Adenovirus pneumonia was associated with the highest sequelae risk (54.8% [39.2-70.5%]) but children hospitalised with no pathogen isolated also had high risk (17.6% [10.9-24.3%]). The most common type of major sequela was restrictive lung disease (5.4% [2.5-10.2%]) . Potential confounders such as loss to follow up and median age at infection were not associated with sequelae risk in the final models., CONCLUSIONS: All children with pneumonia diagnosed by a health professional should be considered at risk of long term sequelae. Evaluation of childhood pneumonia interventions should include potential impact on long term respiratory sequelae

El-Zein M, Parent ME, Benedetti A, Rousseau MC. Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. Int J Epidemiol 2010;39(2):469-86.

Abstract: BACKGROUND: Results have been conflicting as to whether Bacillus Calmette-Guerin (BCG) vaccine, a non-specific stimulator of the immune function, protects, predisposes or is unrelated to the development of childhood asthma. In this systematic review and meta-analysis, we qualitatively and quantitatively appraised the epidemiological evidence., METHODS: Eligible studies were identified using a search strategy that included a computerized literature search and a manual search of each article's reference list, up to June 2008. A total of 23 studies were included (10 cohort, 5 case-control and 8 cross-sectional). Each study was summarized and rated for methodological quality. Pooled odds ratio (OR) estimates and 95% confidence intervals (CIs) were calculated using fixed-effects (FE) or random-effects (RE) models; if heterogeneity was present, the latter was used. Three indicators of BCG exposure were considered including BCG vaccination, tuberculin response and scar diameter., RESULTS: The pooled estimate of association for 23 studies reporting on any of the three indicators suggested a protective effect of BCG exposure on childhood asthma occurrence. The studies were heterogeneous, especially when tuberculin response was considered. Restriction to a subgroup of 16 studies that considered BCG vaccination indicated a protective effect with no evidence of heterogeneity. The overall pooled OR using an FE model was 0.86

(95% CI 0.79-0.93). Exclusion of three studies with the lowest quality scores showed a similar association., CONCLUSION: These results strengthen the epidemiological evidence in support of the hypothesis that exposure to the BCG vaccine in early life prevents asthma, possibly through a modulation of the immune maturation process

Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, FitzGerald JM. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. Chest 2009;136(5):1316-23.

Abstract: BACKGROUND: Epidemiologic studies have identified an increased risk of asthma with acetaminophen use, but the results have been conflicting. We sought to quantify the association between acetaminophen use and the risk of asthma in children and adults., METHODS: We searched all the major medical databases, including MEDLINE (from 1966 to 2008) and EMBASE (from 1980 to 2008) to identify pertinent articles. All clinical trials and observational studies were considered. For observational studies, we selected those that clearly defined acetaminophen use and asthma diagnosis. Study quality was assessed by two reviewers, and data were extracted into a spreadsheet. A random-effects model was used to combine studies with asthma and wheezing among both children and adults., RESULTS: Thirteen cross-sectional studies, four cohort studies, and two case-control studies comprising 425,140 subjects were included in the review. The pooled odds ratio (OR) for asthma among subjects using acetaminophen was 1.63 (95% CI, 1.46 to 1.77). The risk of asthma in children among users of acetaminophen in the year prior to asthma diagnosis and within the first year of life was elevated (OR: 1.60 [95% CI, 1.48 to 1.74] and 1.47 [95% CI, 1.36 to 1.56], respectively). Only one study reported the association between high acetaminophen dose and asthma in children (OR, 3.23; 95% CI, 2.9 to 3.6). There was an increase in the risk of asthma and wheezing with prenatal use of acetaminophen (OR: 1.28 [95% CI, 1.16 to 1.41] and 1.50 [95% CI, 1.10 to 2.05], respectively)., CONCLUSIONS: The results of our review are consistent with an increase in the risk of asthma and wheezing in both children and adults exposed to acetaminophen. Future studies are needed to confirm these results

Marra F, Lynd L, Coombes M, Richardson K, Legal M, FitzGerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma? A systematic review and metaanalysis. 2006. Chest 2009;136(5 Suppl):e30.

Intet abstract.

Mendy A, Gasana J, Vieira ER, Forno E, Patel J, Kadam P, et al. Endotoxin exposure and childhood wheeze and asthma: a meta-analysis of observational studies. J Asthma 2011;48(7):685-93.

Abstract: BACKGROUND: Exposure to endotoxin has been widely investigated as a potential factor for asthma and associated symptoms in children with different results. To clarify a potential relationship, we performed the present meta-analysis to integrate the results of studies examining the association of endotoxin exposure with wheeze and asthma in children., METHODS: A search for relevant studies and reviews was conducted in MEDLINE, Highwire, CINAHL, and The Cochrane Library databases. Adjusted odds ratio (OR) with corresponding 95% confidence interval (CI) for endotoxin exposure and wheeze or asthma were retrieved and pooled to generate summary effect estimates in STATA 11.1., RESULTS: Nineteen studies were included in the meta-analysis.

The summary estimates suggested that endotoxin was positively associated with wheeze in infants and toddlers (meta-OR: 1.48, 95% CI: 1.10-1.98), but negatively related to asthma in school-aged children (meta-OR: 0.82, 95% CI: 0.69-0.97 for endotoxin concentration and 0.68, 95% CI: 0.50-0.93 for endotoxin load)., CONCLUSIONS: Based on the studies evaluated, endotoxin is a risk factor for wheeze in younger children, but a protective factor for asthma in older children. Thus, this study supports the "hygiene hypothesis."

Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. Pediatrics 2011;127(6):1125-38.

Abstract: CONTEXT: The increasing prevalence of childhood asthma has been associated with low microbial exposure as described by the hygiene hypothesis., OBJECTIVE: We sought to evaluate the evidence of association between antibiotic exposure during pregnancy or in the first year of life and risk of childhood asthma., METHODS: PubMed was systematically searched for studies published between 1950 and July 1, 2010. Those that assessed associations between antibiotic exposure during pregnancy or in the first year of life and asthma at ages 0 to 18 years (for pregnancy exposures) or ages 3 to 18 years (for first-year-of-life exposures) were included. Validity was assessed according to study design, age at asthma diagnosis, adjustment for respiratory infections, and consultation rates., RESULTS: For exposure in the first year of life, the pooled odds ratio (OR) for all studies (N = 20) was 1.52 (95% confidence interval [CI]: 1.30-1.77). Retrospective studies had the highest pooled risk estimate for asthma (OR: 2.04 [95% CI: 1.83-2.27]; n = 8) compared with database and prospective studies (OR: 1.25 [95% CI: 1.08-1.45]; n = 12). Risk estimates for studies that adjusted for respiratory infections (pooled OR: 1.16 [95% CI: 1.08-1.25]; n = 5) or later asthma onset (pooled OR for asthma at or after 2 years: OR: 1.16 [95% CI: 1.06-1.25]; n = 3) were weaker but remained significant. For exposure during pregnancy (n = 3 studies), the pooled OR was 1.24 (95% CI: 1.02-1.50)., CONCLUSIONS: Antibiotics seem to slightly increase the risk of childhood asthma. Reverse causality and protopathic bias seem to be possible confounders for this relationship

Patelarou E, Chochlidaki M, Vivilaki V, Brokalaki H. Is there a link between wheezing in early childhood and adverse birth outcomes? A systematic review. Int J Environ Res Public Health 2009;6(11):2752-61.

Abstract: We aimed to provide a summary of the existing published knowledge on the association between adverse birth outcomes and the development of wheezing during the first two years of life. We carried out a systematic review of epidemiological studies within the MEDLINE database. Epidemiological studies on human subjects, published in English, were included in the review. A comprehensive literature search yielded 72 studies for further consideration. Following the application of the eligibility criteria we identified nine studies. A positive association and an excess risk of wheezing during the first two years of life were revealed for adverse birth outcomes

Penders J, Kummeling I, Thijs C. Infant antibiotic use and wheeze and asthma risk: a systematic review and meta-analysis. Eur Respir J 2011;38(2):295-302.

Abstract: Our aim was to systematically review and meta-analyse longitudinal studies on antibiotic use and subsequent development of wheeze and/or asthma with regards to study quality, outcome measurement, reverse causation (RC; wheezing/asthma symptoms have caused prescription of antibiotics) and confounding by indication (CbI; respiratory tract infections leading to antibiotic use may be the underlying cause triggering asthma symptom development). English-language papers and studies published

before November 1, 2010 with longitudinal observational design were included. Study quality was assessed using the Newcastle-Ottawa scale. We identified 21 longitudinal studies. The effect of antibiotic use on wheeze/asthma risk varied between studies. 18 studies were eligible for meta-analysis showing pooled OR 1.27 (95% CI 1.12-1.43) for wheeze/asthma. When we eliminated studies with possible RC and CbI, the pooled risk estimate in the nine remaining studies was attenuated to OR 1.12 (95% CI 0.98-1.26). Definition of wheeze/asthma and age at follow-up differed between studies. Three studies focused on wheeze/asthma beyond 5-6 yrs of age with the presence of active symptoms and/or medication (pooled OR 1.08, 95% CI 0.93-1.23; dominated by one study). RC and CbI lead to overestimation of the association between antibiotic use and subsequent development of wheeze/asthma. Association was weak when fully adjusted for these types of bias. Heterogeneity of disease definition between studies could affect the results

Shiotani A, Kamada T, Kusunoki H, Hata J, Haruma K. [[Helicobacter pylori infection and allergic diseases](#)]. *Nippon Rinsho* 2009;67(12):2352-6.

Abstract: The prevalence of airway allergic diseases has increased in developed countries including Japan. There is a much published potential link between allergy and childhood infection. In 1989, Strachan proposed "hygiene hypothesis" that infections and living in an unhygienic environment might prime the immune system and thus protect against the development of allergic diseases. *H. pylori* would suppress allergic immune-mediated inflammation through T helper type 1 (Th1)/Th2 paradigm, which is suppression of Th2 responses by stimulation of Th1 immunity. In contrast, *H. pylori* infection has been associated with extra-digestive pathologies including chronic idiopathic urticaria. Although systematic review demonstrated that eradication was associated with remission of urticaria, the association is still controversial and the pathogenic mechanisms have never been confirmed

Thong BYH, Tan TC. [Epidemiology and risk factors for drug allergy](#). *Br J Clin Pharmacol* 2011;71(5):684-700.

Abstract: The aim of this review was to describe the current evidence-based knowledge of the epidemiology, prevalence, incidence, risk factors and genetic associations of drug allergy. Articles published between 1966 and 2010 were identified in MEDLINE using the key words adult, adverse drug reaction reporting systems, age factors, anaphylactoid, anaphylaxis, anaesthetics, antibiotics, child, drug allergy, drug eruptions, ethnic groups, hypersensitivity, neuromuscular depolarizing agents, neuromuscular nondepolarizing agents, sex factors, Stevens Johnson syndrome and toxic epidermal necrolysis. Additional studies were identified from article reference lists. Relevant, peer-reviewed original research articles, case series and reviews were considered for review. Current epidemiological studies on adverse drug reactions (ADRs) have used different definitions for ADR-related terminology, often do not differentiate immunologically and non-immunologically mediated drug hypersensitivity, study different study populations (different ethnicities, inpatients or outpatients, adults or children), utilize different methodologies (spontaneous vs. non-spontaneous reporting, cohort vs. case-control studies), different methods of assessing drug imputability and different methods of data analyses. Potentially life-threatening severe cutaneous adverse reactions (SCAR) are associated with a high risk of morbidity and mortality. HLA associations for SCAR associated with allopurinol, carbamazepine and abacavir have been reported with the potential for clinical use in screening prior to prescription. Identification of risk factors for drug allergy and appropriate genetic screening of at-risk ethnic groups may improve the outcomes of drug-specific SCAR. Research and collaboration are necessary for the

generation of clinically-relevant, translational pharmacoepidemiological and pharmacogenomic knowledge, and success of health outcomes research and policies on drug allergies.

Faktorer knyttet til barnets ernæring.

Studiene omfatter hvordan ulike typer mat og kosttilskudd påvirker forekomst av allergi, men også bruk av smokk og betydningen av BMI. Oversiktene er sortert alfabetisk etter førsteforfatter.

Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. J Pediatr Gastroenterol Nutr 2010;50(4):422-30.

Abstract: OBJECTIVE: A reduced risk of atopic dermatitis (AD) among healthy infants who received 100% whey protein partially hydrolyzed formula (PHF-W) compared with intact protein cow's milk formula (CMF), has been reported in several studies. To validate these observations and estimate the magnitude of this potential association with greater statistical precision, we conducted a meta-analysis of clinical trial and intervention studies., MATERIALS AND METHODS: A total of 18 articles representing 12 independent study populations met our inclusion criteria., RESULTS: A statistically significant 44% (summary relative risk estimate [SRRE] = 0.56, 95% confidence interval 0.40-0.77) reduced risk of atopic manifestations, which included AD, was found among infants receiving PHF-W compared with infants receiving CMF. In a subanalysis of 4 studies that reported results specifically for AD and that were considered of superior methodological quality, the incidence of AD was reduced by 55% (SRRE = 0.45, 95% confidence interval 0.30-0.70)., CONCLUSIONS: Regardless of study design, infant population, follow-up time, or study location, individual study findings were consistent because a reduced incidence of AD was reported in all of the reviewed studies. Exclusive breast-feeding should be encouraged as the standard for infant nutrition in the first months of life. For infants who are not exclusively breast-fed, feeding with PHF-W instead of CMF reduces the risk of AD in infants, particularly in infants with a family history of allergy

Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy 2009;64(6):840-8.

Abstract: RECORD STATUS: This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn

AUTHOR'S OBJECTIVES: To evaluate the effectiveness of omega 3 and 6 oils in the primary prevention of sensitisation, eczema or atopic dermatitis, allergic rhinitis, asthma, and other allergic disorders

SEARCHING: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, PsycINFO, AMED, and Web of Science were searched and Google Scholar was used to search the Internet, with dates spanning from 1966 to 2008. The bibliographies of relevant studies were scanned for additional material. Unpublished and ongoing trials were sought from the meta Register of Controlled Trials, ClinicalTrials.gov, and the NRR. Manufacturers and field experts were also contacted for further studies. There were no language restrictions

VALIDITY ASSESSMENT: Trial quality was assessed using the following Cochrane criteria: allocation concealment, method of treatment allocation, reporting of exclusions, completeness of follow-up, and reporting of complications. Each parameter was scored as A (low risk of bias), B (moderate risk of bias), or C (high risk of bias), and an overall assessment was recorded for each trial. The Jadad quality assessment tool was also used to assess allocation concealment, blinding, and withdrawals. Trials were scored from 0 (low quality) to 5 (high quality). Two independent reviewers assessed the quality of the included trials

DATA EXTRACTION: Data were extracted to calculate relative risks (RRs) and 95% confidence intervals (CIs). This was carried out by one reviewer and checked by a second reviewer. Disagreements were resolved by discussion, or by arbitration with a third reviewer

RESULTS OF THE REVIEW: Six RCTs were included in the review (n=938 participants). Four trials (n=679) compared omega 3, and two trials (n=259) compared omega 6, with placebo. A further eight on-going trials were found, the details of which were reported in the paper. Trial quality was scored A (Cochrane) and 5 (Jadad) in five trials; and B and 3 in one trial. The meta-analysis showed that there were no statistically significant benefits in favour of omega 3 or 6 supplementation on any outcome relating to eczema or atopic dermatitis, asthma, allergic rhinitis, or food allergy. The results of other analyses were inconsistent in the development of sensitisation to common allergens, with only one trial reporting a statistically significant effect of omega 6 supplementation on lowering serum immunoglobulin E levels ($p < 0.01$) in atopic participants. Omega 3 supplementation was associated with statistically significant benefits in immunological response, but the effects were either short term or inconsistent

AUTHOR'S CONCLUSION: Supplementation with omega 3, 6, or both was unlikely to prevent sensitisation or allergic disease

CRD COMMENTARY: The review question was clear and this was supported by potentially reproducible inclusion criteria. The search strategy included some relevant sources, and there were clear efforts to minimise language and publication biases. The review process was conducted with sufficient attempts to minimise error and bias. An appropriate validity assessment was carried out, and the results of this indicated the high quality of the included trials. Other study details were reported adequately, including those for a number of on-going trials. Heterogeneity was assessed, and the chosen methods of synthesis appeared to be appropriate. This was a well-conducted review and the authors' conclusions appear to be reliable for the population under investigation

IMPLICATIONS OF THE REVIEW FOR PRACTICE AND RESEARCH: Research: The authors stated that future trials should build on the findings of this review, ensuring that mechanistic, clinical, and health service endpoints are considered. Practice: The authors stated that omega 3 and 6 supplementation could not be recommended for the prevention of allergic disease

Batchelor JM, Grindlay DJC, Williams HC. What's new in atopic eczema? An analysis of systematic reviews published in 2008 and 2009. Clin Exp Dermatol 2010;35(8):823-8.

Abstract: This review summarizes clinically important findings from nine systematic reviews of the causes, treatment and prevention of atopic eczema (AE) published between August 2008 and August 2009. Two systematic reviews concluded that there is a strong and consistent association between filaggrin (FLG) mutations and development of eczema. The associations between FLG mutations and atopic sensitization, rhinitis and asthma are weaker than between FLG mutations and eczema, especially if those who also have eczema are excluded. The relationship between transforming growth factor levels in breast milk and eczema development is still unclear. A further systematic review found no strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against eczema, even in those with a positive family history of atopy. Based on a systematic review and meta-analysis of six randomized controlled trials,

supplementation with omega-3 and omega-6 oils is unlikely to play an important role in the primary prevention of eczema or allergic diseases in general. There is little evidence to support dietary restrictions of certain foods in unselected children with AE. There is also little evidence to suggest a clinically useful benefit from using probiotics in patients with established eczema. A systematic review of topical pimecrolimus and tacrolimus added little additional information to previous reviews, and did not provide any new data on long-term safety. Both of these drugs work in AE, and may reduce flares and usage of topical corticosteroids; however, there is still uncertainty about how they compare with topical corticosteroids.

Brew BK, Allen CW, Toelle BG, Marks GB. Systematic review and meta-analysis investigating breast feeding and childhood wheezing illness. Paediatr Perinat Epidemiol 2011;25(6):507-18.

Abstract: There is conflicting evidence concerning the relationship between breast feeding and wheezing illness. The objective of this study was to investigate whether there is any association between breast feeding and wheezing in children aged over 5 years and to discover possible sources of heterogeneity. An electronic search of MEDLINE and EMBASE databases was conducted from January 2000 to June 2010. In addition, reference lists from relevant publications were searched. Birth cohort, cross-sectional and case-control studies were included if they measured any breast feeding or exclusive breast feeding for 3 or 4 months. Wheezing illness, including asthma, was identified based on symptoms, reported diagnosis or objective criteria. Thirty-one publications were identified for meta-analysis. There was no association found between any or exclusive breast feeding and wheezing illness, although there was a high level of heterogeneity between the studies. Subgroup analysis revealed that any breast feeding slightly lowers the odds of wheeze (pooled odds ratio 0.92 [0.86, 0.98]) but slightly increases the odds of asthma defined by specific criteria (pooled odds ratio 1.10 [1.00, 1.22]). This meta-analysis does not provide evidence that breast feeding is protective against wheezing illness in children aged 5 years and over. The difference in the effects of breast feeding according to the nature of the wheezing illness highlights the importance of the heterogeneity of illness phenotypes.

Castilho SD, Rocha MAM. Pacifier habit: history and multidisciplinary view. J Pediatr (Rio J) 2009;85(6):480-9.

Abstract: OBJECTIVES: To review the history of pacifiers and to compile a multidisciplinary literature review, searching for pros and cons with the purpose of providing health professionals with arguments when parents request guidance., SOURCES: History and art books, as well as non-medical literature and museums were used in the historical survey. Multidisciplinary data were collected from MEDLINE, LILACS, SciELO, and The Cochrane Library. Search criteria were: the keyword "pacifiers" present in articles published in the last 5 years that included abstract and were written in Portuguese, English, or Spanish., SUMMARY OF THE FINDINGS: There is evidence that their precursors have been used since the Neolithic Period to calm down children. Small balls made of fabric containing food were portrayed in paintings. Other balls made of non-perishable material persisted throughout time. Pacifiers have been used to stimulate sucking or to coordinate this reflex, promoting an earlier beginning of the oral feeding of newborns. Some authors suggest that pacifiers reduce the incidence of the sudden death syndrome, but the topic is controversial. Pacifiers prevent the establishment of breastfeeding and lead to weaning. Their use may cause suffocation, poisoning, or allergies and increases the risk of caries, infections, and intestinal parasitic diseases. Harmful effects are related to frequency, duration, and intensity of the habit. It should be discontinued by the age of 3 or 4 in order not to affect speech and dentition., CONCLUSIONS: There are more harmful effects than benefits. It is advisable that health pro-

professionals inform parents of the pros and cons of pacifiers so that they can make a conscious decision regarding its use

Chafen JJS, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, et al. Diagnosing and managing common food allergies: a systematic review. JAMA 2010;303(18):1848-56.

Abstract: CONTEXT: There is heightened interest in food allergies but no clear consensus exists regarding the prevalence or most effective diagnostic and management approaches to food allergies., OBJECTIVE: To perform a systematic review of the available evidence on the prevalence, diagnosis, management, and prevention of food allergies., DATA SOURCES: Electronic searches of PubMed, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials. Searches were limited to English-language articles indexed between January 1988 and September 2009., STUDY SELECTION: Diagnostic tests were included if they had a prospective, defined study population, used food challenge as a criterion standard, and reported sufficient data to calculate sensitivity and specificity. Systematic reviews and randomized controlled trials (RCTs) for management and prevention outcomes were also used. For foods where anaphylaxis is common, cohort studies with a sample size of more than 100 participants were included., DATA EXTRACTION: Two investigators independently reviewed all titles and abstracts to identify potentially relevant articles and resolved discrepancies by repeated review and discussion. Quality of systematic reviews and meta-analyses was assessed using the AMSTAR criteria, the quality of diagnostic studies using the QUADAS criteria most relevant to food allergy, and the quality of RCTs using the Jadad criteria., DATA SYNTHESIS: A total of 12,378 citations were identified and 72 citations were included. Food allergy affects more than 1% to 2% but less than 10% of the population. It is unclear if the prevalence of food allergies is increasing. Summary receiver operating characteristic curves comparing skin prick tests (area under the curve [AUC], 0.87; 95% confidence interval [CI], 0.81-0.93) and serum food-specific IgE (AUC, 0.84; 95% CI, 0.78-0.91) to food challenge showed no statistical superiority for either test. Elimination diets are the mainstay of therapy but have been rarely studied. Immunotherapy is promising but data are insufficient to recommend use. In high-risk infants, hydrolyzed formulas may prevent cow's milk allergy but standardized definitions of high risk and hydrolyzed formula do not exist., CONCLUSION: The evidence for the prevalence and management of food allergy is greatly limited by a lack of uniformity for criteria for making a diagnosis

Delgado-Noguera MF, Calvache JA, Bonfill Cosp X. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. Cochrane Database Syst Rev 2010;(12):CD007901.

Abstract: BACKGROUND: Long chain polyunsaturated fatty acids (LCPUFA), especially docosahexaenoic acid (DHA), are the most abundant fatty acids in the brain and are necessary for growth and maturation of the brain and retina. LCPUFA are named "essential" because they cannot be synthesised efficiently by the human body and come from maternal diet. It remains controversial whether LCPUFA supplementation to breastfeeding mothers is beneficial for the development of their infants., OBJECTIVES: To assess the effectiveness and safety of supplementation with LCPUFA in breastfeeding mothers in the cognitive and physical development of their infants as well as safety for the mother and infant., SEARCH STRATEGY: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (November 2009), CENTRAL (2009, Issue 2), PubMed (1966 to July 2009), EMBASE (1974 to June 2009), CINAHL (1984 to June

2009), LILACS (1982 to June 2009), Google Scholar (June 2009) and reference lists of published narrative and systematic reviews., SELECTION CRITERIA: Randomised controlled trials or cluster-randomised controlled trials evaluating the effects of LCPUFA supplementation on breastfeeding mothers and their infants., DATA COLLECTION AND ANALYSIS: Two review authors independently assessed eligibility and trial quality and performed data extraction., MAIN RESULTS: We included six randomised controlled trials involving 1280 women. We found no significant difference in children's neurodevelopment: language development (standardised mean difference (SMD) -0.14, 95% confidence interval (CI) -0.49 to 0.20; two trials, 349 participants); intelligence or problem-solving ability (two trials, 817 participants; SMD -0.22, 95% CI -0.23 to 0.66); psychomotor development (SMD 0.34, 95% CI -0.11 to 0.78; two trials, 279 participants); motor development (SMD 0.08, 95% CI -0.13 to 0.29; two trials, 349 participants); in child attention there was a significant difference (SMD 0.50, 95% CI 0.24 to 0.77; one study). For child visual acuity there was no significant difference (SMD -0.06, 95% CI -0.26 to 0.14; three trials, 401 participants). For growth, there were significant differences in length (MD -0.75 cm, 95% CI -1.38 to -0.12; two trials, 834 participants) and head circumference (MD 0.69 cm, 95% CI 0.35 to 1.02; one trial, 244 participants). One study reported a significant difference in infant allergy (risk ratio (RR) 0.12, 95% CI 0.02 to 0.95). We found no significant difference in one trial evaluating postpartum depression (SMD 0.15, 95% CI -0.11 to 0.41). [NON-BREAKING SPACE], AUTHORS' CONCLUSIONS: Based on the limited evidence that we found, LCPUFA supplementation did not appear to improve children's neurodevelopment or visual acuity. In two studies, LCPUFA supplementation was associated with increased head circumference. Currently, there is insufficient evidence to support or refute the practice of giving LCPUFA supplementation to breastfeeding mothers in order to improve infant growth and development

Flohr C, Nagel G, Weinmayr G, Kleiner A, Strachan DP, Williams HC, et al. Lack of evidence for a protective effect of prolonged breastfeeding on childhood eczema: lessons from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two.

Br J Dermatol 2011;165(6):1280-9.

Abstract: BACKGROUND: Exclusive breastfeeding for at least 4 months is recommended by many governments and allergy organizations to prevent allergic disease., OBJECTIVES: To investigate whether exclusive breastfeeding protects against childhood eczema., METHODS: Study subjects comprised 51,119 randomly selected 8- to 12-year-old schoolchildren in 21 countries. Information on eczema and breastfeeding was gathered by parental questionnaire. Children were also examined for flexural eczema and underwent skin prick testing. Odds ratios (ORs) were calculated for each study centre and then pooled across populations., RESULTS: There was a small increase in the risk of reported 'eczema ever' in association with 'breastfeeding ever' and breastfeeding < 6 months [pooled adjusted OR 1.11, 95% confidence interval (CI) 1.00-1.22 and OR 1.10, 95% CI 1.02-1.20, respectively]. There was no significant association between reported 'eczema ever' and breastfeeding > 6 months (pooled adjusted OR 1.09, 95% CI 0.94-1.26). Risk estimates were very similar for exclusive breastfeeding < 2 months, 2-4 months and > 4 months and for eczema symptoms in the past 12 months and eczema on skin examination. As for more severe eczema, breastfeeding per se conveyed a risk reduction on sleep disturbed eczema (pooled adjusted OR 0.71, 95% CI 0.53-0.96), but this effect was lost where children had been exclusively breastfed for > 4 months (pooled adjusted OR 1.02, 95% CI 0.67-1.54). Allergic sensitization and a history of maternal allergic disease did not modify any of these findings., CONCLUSIONS: Although there was a protective effect of ever having been breastfed on more severe disease, we found no evidence that exclusive breastfeeding for 4 months or longer protects against eczema. Our results are consistent with findings from a recent systematic review of

prospective studies. The U.K. breastfeeding guidelines with regard to eczema should be reviewed. Intervention studies are now required to explore how and when solids should be introduced alongside breastfeeding to aid protection against eczema and other allergic diseases.

Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. Overview of Reviews The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evidence-based child health : a Cochrane review journal 2011;6(5):1322-39.

Abstract: **BACKGROUND:** Eczema is the most common inflammatory skin disease of childhood, characterized by an itchy red rash that usually involves the face and skin folds. There is currently no curative treatment for eczema, so the reduction of eczema incidence through disease prevention is a desirable goal. Potential interventions for preventing eczema include exclusive breastfeeding, hydrolysed protein formulas and soy formulas when bottle feeding, maternal antigen avoidance, omega oil supplementation, prebiotics and probiotics. **OBJECTIVES:** This overview of reviews aims to present the current body of data from Cochrane and non-Cochrane reviews to provide the most up-to-date evidence on the efficacy and safety of interventions to prevent eczema in infants and children at different risk levels for developing allergic disease. **METHODS:** Our pool of Cochrane and non-Cochrane reviews came from the 2010 United Kingdom National Health Service (NHS) Evidence Skin Disorders Annual Evidence Updates Mapping Exercise on Atopic Eczema. This group used a comprehensive search strategy last conducted in August 2010 to identify all systematic reviews on eczema prevention. We identified all reviews that met our pre-specified inclusion criteria, and data were extracted, analysed, compiled into tables and synthesized using quantitative and qualitative methods. **MAIN RESULTS:** Seven systematic reviews containing 39 relevant trials with 11 897 participants were included in this overview. Overall, there was no clear evidence that any of the main interventions reviewed reduced eczema incidence. In subgroup analyses of infants at high risk of allergic disease, an observational study found that exclusive breastfeeding for at least six months compared with introduction of solids at three to six months decreased the incidence of eczema by 60% (risk ratio (RR): 0.40; 95% confidence interval (CI): 0.21, 0.78), and a randomized controlled trial found that prebiotics compared with no prebiotics decreased incidence by 58% (RR: 0.42; 95% CI: 0.21, 0.84). However, each of these findings was based on the results of a single small trial, and no intervention reduced eczema incidence beyond the first two years of life. Although we pre-specified incidence of atopic eczema (i.e. eczema associated with immunoglobulin E (IgE) sensitization) as a primary outcome, data on whether participants diagnosed with eczema were truly atopic were largely lacking from systematic reviews. Similarly, data on atopy, measured using skin prick tests or specific IgE tests to allergens, were not reported in many reviews. No interventions were found to decrease atopy when reported. Adverse events data were generally lacking, but data from a trial of probiotics versus no probiotics showed significantly more spitting up in the first one (RR: 1.88; 95% CI: 1.03, 3.45) and two (RR: 1.69; 95% CI: 1.02, 2.80) months of life, but no overall increase in risk of gastrointestinal symptoms in the first year. **AUTHORS**#ENTITYSTARTX02019; **CONCLUSIONS:** Although there is currently no clear evidence showing that any of the interventions examined in this overview prevent eczema in participants not selected for risk of allergic disease, there is some evidence that exclusive breastfeeding for at least six months and prebiotics might reduce eczema incidence in high-risk participants. However, these conclusions are based on limited evidence with methodological shortcomings. Future research on prevention of eczema is needed and should examine different types of hydrolysed formulas, prebiotics and probiotics, as well as enhancement of the skin barrier and other novel approaches in infants at different risk levels for developing allergic disease

Greenhawt M. The role of food allergy in atopic dermatitis. Allergy Asthma Proc 2010;31(5):392-7.

Abstract: Atopic dermatitis (AD) affects ~10% of children. Food allergy is a known provoking cause of AD in a subset of affected children. A literature search of PubMed and Medline was conducted to review the epidemiology and pathophysiology of AD, with special focus on the role of food allergy in the development of AD, its management, and its long-term preventive strategies. A literature search of PubMed and Medline was conducted. Food allergens readily provoke AD in ~35% of patients, as proven through double-blind placebo-controlled food challenge studies. Milk, egg, wheat, soy, and peanut account for 75% of the cases of food-induced AD. However, the positive predictive values of the parental history, skin-prick tests, or serum tests for detecting food-specific IgE are low, making these unsuitable for use as single diagnostic modalities. Therefore, the use of a food challenge test is very helpful in objectively confirming the history or positive tests. Elimination diets are often helpful in challenge-proven cases, but care must be taken to evaluate the nutritional status of the child. There are few effective long-term strategies to prevent the development of food allergen-induced AD. Early onset of AD has been shown to be a risk factor for the development of other allergic diseases, including other food allergy/sensitization, as part of the atopic march. Treatment of other causes of AD, such as barrier dysfunction and cutaneous infection, are of equal importance to food allergen avoidance. Food allergy is an important provoking cause of AD, but it is only relevant in ~35% of affected individuals

Ip S, Chung M, Raman G, Trikalinos TA, Lau J. A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. Breastfeed Med 2009;4 Suppl 1:S17-S30.

Abstract: OBJECTIVES: This article summarizes the Agency for Healthcare Research and Quality's evidence report on the effects of breastfeeding on term infant and maternal health outcomes in developed countries. EVIDENCE REPORT DATA SOURCES: Medline, CINAHL, Cochrane Library, bibliographies of selected reviews, and suggestions from domain experts were surveyed. Searches were limited to English-language publications. EVIDENCE REPORT REVIEW METHODS: Eligible comparisons examined the association between differential exposure to breastfeeding and health outcomes. We assessed 15 infant and six maternal outcomes. For four outcomes, we also updated previously published systematic reviews. For the rest of the outcomes, we either summarized previous systematic reviews or conducted new systematic reviews; randomized and non-randomized comparative trials, prospective cohorts, and case-control studies were included. Adjusted estimates were extracted from non-experimental designs. The studies were graded for methodological quality. We did not draw conclusions from poor quality studies. EVIDENCE REPORT RESULTS: We screened over 9,000 abstracts. Thirty-two primary studies on term infant health outcomes, 43 primary studies on maternal health outcomes, and 28 systematic reviews or meta-analyses that covered approximately 400 individual studies were included in this review. A history of breastfeeding was associated with a reduction in the risk of acute otitis media, nonspecific gastroenteritis, severe lower respiratory tract infections, atopic dermatitis, asthma (young children), obesity, type 1 and 2 diabetes, childhood leukemia, and sudden infant death syndrome. There was no relationship between breastfeeding in term infants and cognitive performance. There were insufficient good quality data to address the relationship between breastfeeding and cardiovascular diseases and infant mortality. For maternal outcomes, a history of lactation was associated with a reduced risk of type 2 diabetes, breast, and ovarian cancer. Early cessation of breastfeeding or no breastfeeding was associated with an increased risk of maternal postpartum depression. There

was no relationship between a history of lactation and the risk of osteoporosis. The effect of breastfeeding in mothers on return-to-prepregnancy weight was negligible, and the effect of breastfeeding on postpartum weight loss was unclear. EVIDENCE REPORT CONCLUSIONS: A history of breastfeeding is associated with a reduced risk of many diseases in infants and mothers. Future research would benefit from clearer selection criteria, definitions of breastfeeding exposure, and adjustment for potential confounders. Matched designs such as sibling analysis may provide a method to control for hereditary and household factors that are important in certain outcomes

Iskedjian M, Szajewska H, Spieldenner J, Farah B, Berbari J. Meta-analysis of a partially hydrolysed 100%-whey infant formula vs. extensively hydrolysed infant formulas in the prevention of atopic dermatitis. *Curr Med Res Opin* 2010;26(11):2599-606.

Abstract: OBJECTIVES: This study presents previously unpublished point and cumulative incidence rates and relative risks (RRs) for comparing a partially hydrolysed 100% whey-based infant formula, NAN-HA * (PHF-W) to extensively hydrolysed whey- (EHF-Whey) or casein-based (EHF-Casein) infant formulas in the prevention of atopic dermatitis (AD) in infants who cannot be breastfed exclusively. It also outlines methods to convert the above-mentioned data as well as data comparing PHF-W to cows' milk formula (SF) into inputs to be applied to a pharmacoeconomic model. * NAN-HA is a registered trade name of Nestle SA, Switzerland., METHODS: The incidence rates and RRs were obtained from a meta-analysis which analysed efficacy for PHF-W vs. EHF but did not present those. It took into consideration any relevant randomized controlled trial which compared the use of PHF-W with SF or EHF for the prevention of allergies. The primary outcomes of interest were the incidence, cumulative incidence and period prevalence of allergic manifestations and of AD in particular. Fifteen studies had been included for analysis of which six studies explored PHF-W vs. EHF. These results and PHF-W vs. SF data were adapted for inputs into a pharmacoeconomic model which used a spreadsheet decision-analytic economic model based on 3-month cycles to explore the cost-effectiveness of PHF-W vs. SF and EHF. Weights were applied to the incidence rates and RRs for each reported time period which were then adapted into 3-month indicators., RESULTS: This meta-analysis for PHF-W (557 patients) vs. EHF-Whey (559 patients) yielded RR of 0.75 (0.54, 1.05) and 0.80 (0.63, 1.02) at 0-12 months and at 0-36 months, respectively. Corresponding RRs for PHF-W vs. EHF-Casein (580 patients) were 1.06 (0.74, 1.53) at 0-12 months and 1.13 (0.87, 1.47) at 0-36 months., CONCLUSION: It appears that the efficacy of PHF-W falls within the range of that of both EHF formulas (whey and casein) and allows the application of these results in a pharmacoeconomic model

Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. *Clin Rev Allergy Immunol* 2011;41(1):36-66.

Abstract: There are two main families of polyunsaturated fatty acids (PUFAs), the n-6 and the n-3 families. It has been suggested that there is a causal relationship between n-6 PUFA intake and allergic disease, and there are biologically plausible mechanisms, involving eicosanoid mediators of the n-6 PUFA arachidonic acid, that could explain this. Fish and fish oils are sources of long-chain n-3 PUFAs and these fatty acids act to oppose the actions of n-6 PUFAs. Thus, it is considered that n-3 PUFAs will protect against atopic sensitization and against the clinical manifestations of atopy. Evidence to examine this has been acquired from epidemiologic studies investigating associations between fish intake in pregnancy, lactation, infancy, and childhood, and atopic outcomes in infants and children and from intervention studies with fish oil supplements

in pregnancy, lactation, infancy, and childhood, and atopic outcomes in infants and children. All five epidemiological studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associations. One study investigating the effects of maternal fish intake during lactation did not observe any significant associations. The evidence from epidemiological studies investigating the effects of fish intake during infancy and childhood on atopic outcomes in those infants or children is inconsistent, although the majority of the studies (nine of 14) showed a protective effect of fish intake during infancy or childhood on atopic outcomes in those infants/children. Fish oil supplementation during pregnancy and lactation or during infancy or childhood results in a higher n-3 PUFA status in the infants or children. Fish oil provision to pregnant women is associated with immunologic changes in cord blood and such changes may persist. Studies performed to date indicate that provision of fish oil during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hay fever, and asthma. Fish oil provision to infants or children may be associated with immunologic changes in the blood but it is not clear if these are of clinical significance and whether they persist. Fish oil supplementation in infancy may decrease the risk of developing some manifestations of allergic disease, but this benefit may not persist as other factors come into play. It is not clear whether fish oil can be used to treat children with asthma as the two studies conducted to date give divergent results. Further studies of increased long-chain n-3 PUFA provision in during pregnancy, lactation, and infancy are needed to more clearly identify the immunologic and clinical effects in infants and children and to identify protective and therapeutic effects and their persistence

Maas T, Kaper J, Sheikh A, Knottnerus JA, Wesseling G, Dompeling E, et al. Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma. Cochrane Database Syst Rev 2009;(3):CD006480.

Abstract: BACKGROUND: Allergen exposure is one of the environmental factors seemingly associated with the development of asthma. If asthma is a multi-factorial disease, it is hypothesised that prevention might only prove effective if most or all relevant environmental factors are simultaneously avoided., OBJECTIVES: To assess effect(s) of monofaceted and multifaceted interventions compared with control interventions in preventing asthma and asthma symptoms in high risk children., SEARCH STRATEGY: We searched the Cochrane Airways Trials Register (December 2008)., SELECTION CRITERIA: Randomised controlled trials of allergen exposure reduction for the primary prevention of asthma in children. Interventions were multifaceted (reducing exposure to both inhalant and food allergens) or monofaceted (reducing exposure to either inhalant or food allergens) Follow up had to be from birth (or during pregnancy) up to a minimum of two years of age., DATA COLLECTION AND ANALYSIS: We included in the analysis studies assessing the primary outcome (current diagnosis: asthma) and/or one of the secondary outcomes (current respiratory symptoms: wheezing, nocturnal coughing and dyspnoea). We pooled multifaceted and monofaceted intervention trials separately. We made an indirect comparison of their effects using tests for interaction to calculate relative odds ratios., MAIN RESULTS: We included three multifaceted and six monofaceted intervention studies (3271 children). Physician diagnosed asthma in children less than five years, and asthma as defined by respiratory symptoms and lung function criteria in children aged five years and older, both favoured treatment with a multifaceted intervention compared to usual care (< 5 years: odds ratio (OR) 0.72, 95% confidence interval (CI) 0.54 to 0.96, and > 5 years: OR 0.52, 95% CI 0.32 to 0.85). However, there was no significant difference in outcome between mono-

faceted intervention and control interventions (< 5 years: OR 1.12, 95% CI 0.76 to 1.64, and > 5 years: OR 0.83, 95% CI 0.59 to 1.16). Indirect comparison between these treatments did not demonstrate a significant difference between multiple interventions and mono-interventions in reducing the frequency of asthma diagnosis in children under five years (relative OR 0.64 (95% CI 0.40 to 1.04, P = 0.07) or five years and older (relative OR 0.63, 95% CI 0.35 to 1.13, P = 0.12). There was also no significant difference between either mono- and multifaceted intervention and control in reducing the likelihood of symptoms of nocturnal coughing at follow up. Wheezing, however, showed a significant difference between multifaceted and mono-interventions (relative OR 0.59, 95% CI 0.35 to 0.99, P = 0.04), but the significance was lost when data on treatment only was analysed.

AUTHORS' CONCLUSIONS: The available evidence suggests that the reduction of exposure to multiple allergens compared to usual care reduces the likelihood of a current diagnosis of asthma in children (at ages < 5 years and 5 years and older). Mono-intervention studies have not produced effects which are statistically significant compared with control. In children who are at risk of developing childhood asthma, multifaceted interventions, characterised by dietary allergen reduction and environmental remediation, reduce the odds of a physician diagnosis of asthma later in childhood by half. This translates to a number needed to treat (NNT) of 17. The effect of multi-faceted interventions on parent reported wheeze was inconsistent and had no significant impact on nocturnal coughing or dyspnoea. Data from monofaceted intervention exposed children studies were not significantly different from those of control groups for all outcomes. There remains uncertainty as to whether multiple interventions are more effective than mono-component interventions. The comparisons made were indirect, making the conclusions drawn uncertain. To our knowledge there are no ongoing studies in which both intervention strategies are randomly compared. The findings, however, warrant further direct comparison between multiple- and monofaceted interventions aimed at reducing the prevalence of asthma in children

Mulloy A, Lang R, O'Reilly M, Sigafos J, Lancioni G, Rispoli M. Gluten-free and casein-free diets in the treatment of autism spectrum disorders: a systematic review. *Research in Autism Spectrum Disorders* 2010;4(3):328-39.

Abstract: RECORD STATUS: This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn

AUTHOR'S OBJECTIVES: To investigate the effects of gluten-free and/or casein-free (GFCF) diets in the treatment of autism spectrum disorder (ASD)

SEARCHING: English-language peer-reviewed studies were identified through a search of PsycINFO, Psychology and Behavioural Sciences Collection, ERIC and MEDLINE. Search terms were reported. Search dates were not reported (the authors stated that publication year was not restricted). Journals that had published studies selected for review were handsearched from 2008 to March 2009

VALIDITY ASSESSMENT: Methodological quality was evaluated to assess level of certainty according to criteria of blinding, adequate inter-observer agreement and treatment fidelity measures (20% or more of sessions with 80% or better agreement), operationally defined dependent variables, enough detail to enable replication, limitations regarding controls against alternative explanations for treatment outcomes (such as maturation, concurrent interventions, problems with construct validity). Studies were classified as suggestive (included uncontrolled trials), preponderant (outcomes were assessed to be likely due to the intervention) and conclusive. The authors did not state how many reviewers performed the validity assessment

DATA EXTRACTION: Data on behavioural or biomedical variables were extracted into standard data extraction forms. Behavioural variables included communication (such as nonverbal communication, vocalisations, question asking), stereotypy, play and challeng-

ing behaviour (such as pica, self-injury, aggression and property destruction). Biomedical variables included levels of urinary peptides, relevant enzymes and antibodies. Results were coded as positive where all participants made improvements and there were statistically significant differences between groups, negative where none of the participants made improvements or if there were no statistically significant differences between groups and mixed where some participants improved and others did not. Percentage of non-overlapping data (PND) was calculated for single-subject designs. Repeated measures effect sizes were calculated for group designs. Repeated measures effect sizes were corrected for bias according to the technique developed by Hedges and Olkin. One reviewer extracted data, which were checked by a second reviewer. Discrepancies were resolved through discussion

RESULTS OF THE REVIEW: Fourteen studies (n=188) were included in the review. Sample sizes ranged from one to 50 participants. Overall study quality was poor; all studies that reported positive results were classified at the lowest level of certainty (suggestive). All studies at the second level (preponderant) reported negative results. None of the reviewed studies were assessed as conclusive. Seven studies reported positive results and four reported negative results, two reported mixed results and in one study the effect of the intervention could not be determined. Quantitative summary of results was possible for four studies. Two of the three single-subject studies reported data. PND values were 0% and 3%. Two of the nine group-design studies reported data for which repeated measures effect sizes could be estimated for several dependent variables. Diet treatments were observed to have effect sizes of -1.80, and -0.82 on participants' level of urinary peptides

AUTHOR'S CONCLUSION: Evidence did not support use of gluten-free and/or casein-free diets in the treatment of ASD

CRD COMMENTARY: This review addressed a clear question supported by appropriate inclusion criteria. Relevant databases were searched. The restriction to English-language studies may have contributed to language bias. One database (ERIC) included unpublished studies. Publication bias was not considered in the report. Suitable methods to minimise risk of reviewer error and bias were reported for study selection and data extraction, but not for validity assessment. Results were pooled narratively supported by a table. A thorough discussion of potential biases and sources of heterogeneity was reported. A basic (vote counting) synthesis was conducted, based on whether results were positive, negative or mixed. Details of study designs (such as number and type of groups) and results of individual studies were poorly reported for most studies and few numbers, confidence intervals or p-values were presented, which made it difficult to evaluate the individual results. However, it appeared clear that the studies had very small sample sizes and were of poor quality, so the authors' conclusions appear appropriate in reflecting the limited evidence

IMPLICATIONS OF THE REVIEW FOR PRACTICE AND RESEARCH: Practice: The authors suggested that restrictive diets should be implemented only where a food allergy or intolerance was detected. The authors suggested that should a child with ASD experience acute behavioural changes seemingly associated with changes in diet, practitioners should consider testing the child for allergies and food intolerances and subsequently eliminate identified allergens and irritants from their environment. Research: The authors suggested controlled trials to determine whether a GFCF diet had any additional therapeutic benefit for individual children with ASD

Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan DP, [ISAAC Phase Two Study Group. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood \(ISAAC\) Phase Two.](#) Thorax 2010;65(6):516-22.

Abstract: BACKGROUND: The increasing prevalence of asthma and allergy might be related to diet, particularly in Western countries. A study was undertaken to assess the

association between dietary factors, asthma and allergy in a large international study including objective measurements of atopy., METHODS: Between 1995 and 2005, cross-sectional studies were performed in 29 centres in 20 countries. Parental questionnaires were used to collect information on allergic diseases and exposure factors and data from 50 004 randomly selected schoolchildren (8-12 years, 29 579 with skin prick testing) were analysed. Random effect models for meta-analysis were applied to calculate combined ORs., RESULTS: Fruit intake was associated with a low prevalence of current wheeze in affluent (OR(adj) 0.86, 95% CI 0.73 to 1.02) and non-affluent countries (OR(adj) 0.71, 95% CI 0.57 to 0.88). Consumption of fish in affluent countries (OR(adj) 0.85, 95% CI 0.74 to 0.97) and of cooked green vegetables in non-affluent countries (OR(adj) 0.78, 95% CI 0.65 to 0.95) was associated with a lower prevalence of current wheeze. Overall, more frequent consumption of fruit, vegetables and fish was associated with a lower lifetime prevalence of asthma, whereas high burger consumption was associated with higher lifetime asthma prevalence. None of the food items was associated with allergic sensitisation. Except for fruit juice and fruit consumption, no associations were found with atopic wheeze. Food selection according to the 'Mediterranean diet' was associated with a lower prevalence of current wheeze and asthma ever (p(trend)=0.03)., CONCLUSION: Diet is associated with wheeze and asthma but not with allergic sensitisation in children. These results provide further evidence that adherence to the 'Mediterranean diet' may provide some protection against wheeze and asthma in childhood

Noal RB, Menezes AMB, Macedo SEC, Dumith SC. Childhood body mass index and risk of asthma in adolescence: a systematic review. *Obes Rev* 2011;12(2):93-104.

Abstract: Asthma and obesity, both of which are considered global health issues, affect approximately 300 million individuals worldwide. The observation that asthma and obesity tend to increase in parallel may indicate a potential link between these two conditions. The aim of this systematic review of the literature was to investigate the relationship between childhood nutritional status and incidence or persistence of asthma during adolescence. The principal eligibility criteria for selection of articles were including longitudinal analysis, and which measured of exposure during childhood or adolescence and outcome during adolescence. The systematic search initially returned 1563 unique articles. After inspection of titles and reading the abstracts of these articles, we chose 27 for full reading. Of these, 10 were selected to be included in the present review. Of the 10 selected studies, eight showed positive associations between overweight/obesity and asthma. Of these, two were independent of sex, three were found only among men and another three only among women. The present study shows strong evidence that, although the role of sex is not clear, obesity precedes, and is associated with, the persistence and intensity of symptoms of asthma

Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol* 2011;127(3):724-30.

Abstract: BACKGROUND: Epidemiologic studies suggest that deficiencies of the nutrients selenium; zinc; vitamins A, C, D, and E; and low fruit and vegetable intake may be associated with the development of asthma and allergic disorders., OBJECTIVES: To investigate the evidence that nutrient and food intake modifies the risk of children developing allergy., METHODS: We systematically searched 11 databases. Studies were critically appraised, and meta-analyses were undertaken., RESULTS: We identified 62 eligible reports. There were no randomized controlled trials. Studies used cohort (n = 21), case-control (n = 15), or cross-sectional (n = 26) designs. All studies were judged to be at moderate to substantial risk of bias. Meta-analysis revealed that serum vitamin A was lower in child-

ren with asthma compared with controls (odds ratio [OR], 0.25; 95% CI, 0.10-0.40). Meta-analyses also showed that high maternal dietary vitamin D and E intakes during pregnancy were protective for the development of wheezing outcomes (OR, 0.56, 95% CI, 0.42-0.73; and OR, 0.68, 95% CI, 0.52-0.88, respectively). Adherence to a Mediterranean diet was protective for persistent wheeze (OR, 0.22; 95% CI, 0.08-0.58) and atopy (OR, 0.55; 95% CI, 0.31-0.97). Seventeen of 22 fruit and vegetable studies reported beneficial associations with asthma and allergic outcomes. Results were not supportive for other allergic outcomes for these vitamins or nutrients, or for any outcomes in relation to vitamin C and selenium., CONCLUSION: The available epidemiologic evidence is weak but nonetheless supportive with respect to vitamins A, D, and E; zinc; fruits and vegetables; and a Mediterranean diet for the prevention of asthma. Experimental studies of these exposures are now warranted.

Oddy WH, Rosales F. A systematic review of the importance of milk TGF-beta on immunological outcomes in the infant and young child. *Pediatr Allergy Immunol* 2010;21(1 Pt 1):47-59.

Abstract: Cytokines in milk like transforming growth factor-beta (TGF-beta) have been shown to induce oral tolerance in experimental animal studies. However, human studies are less consistent with these findings. The primary objective of this review was to conduct a systematic review of published studies on the association between TGF-beta identified in human milk and immunological outcomes in infancy and early childhood. Human prospective clinical studies were identified through MEDLINE, CAB Abstracts, Biological Abstracts and Scopus. Selection criteria included: well described populations of mothers and infants, time of milk sampling, immunological outcome measures and analytical methods of TGF-beta determination. We considered a wide range of immunological outcomes in infancy and early childhood, such as wheeze, atopy, eczema and the immunoglobulin switch. Twelve human studies were included in the review and 67% showed a positive association with TGF-beta1 or TGF-beta2 demonstrating protection against allergy-related outcomes in infancy and early childhood. High variability in concentrations of TGF-beta was noted between and within studies, some of it explained by maternal history of atopy or by consumption of probiotics. Human milk TGF-beta appears to be essential in developing and maintaining appropriate immune responses in infants and may provide protection against adverse immunological outcomes, corroborating findings from experimental animal studies. Further large clinical studies in diverse human populations are indicated to confirm these results.

Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology* 2012;23(3):402-14.

Abstract: BACKGROUND: The study of probiotics to prevent allergic conditions has yielded conflicting results in children. We undertook a meta-analysis of randomized controlled trials to investigate whether probiotic use during pregnancy and early life decreases the incidence of atopic dermatitis and immunoglobulin E (IgE)-associated atopic dermatitis in infants and young children., METHODS: We performed a systematic literature search in Medline, Embase, and Cochrane Library, updated to October 2011. The intervention was diet supplementation with probiotics versus placebo. Primary outcomes were incidence of atopic dermatitis and IgE-associated atopic dermatitis. We calculated summary relative risks (RRs) and corresponding 95% confidence intervals (CIs), using both fixed- and random-effects models. We computed summary estimates across several strata, including study period, type of patient, dose, and duration of intervention, and we assessed the risk of bias within and across trials., RESULTS: We identified 18 publications based on 14 studies. Meta-analysis demonstrated that probi-

otic use decreased the incidence of atopic dermatitis (RR = 0.79 [95% CI = 0.71-0.88]). Studies were fairly homogeneous (I = 24.0%). The corresponding RR of IgE-associated atopic dermatitis was 0.80 (95% CI = 0.66-0.96). No appreciable difference emerged across strata, nor was there evidence of publication bias., CONCLUSIONS: This meta-analysis provided evidence in support of a moderate role of probiotics in the prevention of atopic dermatitis and IgE-associated atopic dermatitis in infants. The favorable effect was similar regardless of the time of probiotic use (pregnancy or early life) or the subject(s) receiving probiotics (mother, child, or both)

Schneider Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, et al. Diagnosing and managing common food allergies: a systematic review. JAMA

2010;303(18):1848-56.

Abstract: RECORD STATUS: This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn

AUTHOR'S OBJECTIVES: To assess the prevalence, diagnosis, management and prevention of food allergies

SEARCHING: PubMed, Cochrane Database of Systematic Reviews, DARE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched between 1988 and September 2009 for articles in English. Search terms were reported. The World Allergy Organisation Journal was searched between 1988 and February 2009. Other potentially relevant articles were identified through searching references and contacting experts (this could yield studies from outside the search period)

VALIDITY ASSESSMENT: Diagnostic studies were assessed using QUADAS criteria. Randomised controlled trials (RCTs) of management were assessed using the Jadad scale. Observational studies on management of allergies were initially considered to be of poor quality, but were then rated as good quality if there was a high level of follow-up (≥90%), large sample size (>500 patients) and attempted to reduce bias through study design or statistical analysis. The authors did not state how many reviewers performed the validity assessment

DATA EXTRACTION: For diagnostic studies, sensitivities and specificities were extracted to calculate the summary receiver operator characteristic (ROC) curves, weighted by sample size, and 95% confidence intervals (CIs). It was unclear how many reviewers were involved in data extraction, but discrepancies were resolved through discussion or by referral to a third reviewer

RESULTS OF THE REVIEW: Diagnostic studies (18 prospective studies, n=2,806): Sample sizes ranged between 34 and 495 children. Study quality was reported to be fair; between 11 and 18 studies met 10 of the 12 QUADAS criteria. There were no statistically significant differences between skin prick tests compared with food challenge (AUC 0.87, 95% CI 0.81 to 0.93; 13 studies) or serum food-specific IgE tests compared with food challenge (AUC 0.84, 95% CI 0.78 to 0.91; 11 studies) for all food allergies. There were no statistically significant differences for cow's milk allergy (AUC 0.84, 95% CI: 0.75 to 0.92; eight skin prick test studies and AUC 0.78, 95% CI 0.70 to 0.86; nine serum food-specific IgE test studies) and hen's egg allergy (AUC 0.87, 95% CI 0.76 to 0.97; five skin prick test studies and AUC 0.85, 95% CI 0.62 to 1.09; five serum food-specific IGE test studies). Management studies (25 studies, n=2,006): Sample sizes ranged between 12 and 567. Overall, studies were reported to be of fair quality (seven good, 12 fair and six poor). Studies of oral or subcutaneous immunotherapy reported some improvement on desensitisation compared with controls, but there was insufficient evidence on tolerance and safety (five studies). There was insufficient evidence from studies on food substitutions (three studies) or alterations (five studies) to make definitive conclusions. There was evidence that medical or pharmacologic therapies can improve management of aller-

gies (five studies). One study each assessed elimination diets and low allergen diets and reported improvements in allergies compared with controls. One study reported reduced nut reactions after education. Two studies reported no improvement on outcomes in infants who received probiotics

AUTHOR'S CONCLUSION: Conclusions about best practices for management and prevention of food allergies were greatly hindered by a lack of uniformity of criteria for making a diagnosis

CRD COMMENTARY: The review question was broad and was supported by appropriate inclusion criteria for study design and broad criteria for intervention, comparator, participants and outcomes. The literature search was adequate, but as articles were restricted to English it was possible that language bias may have been introduced. Previously published criteria were used to assess study quality, which was described as fair for both diagnostic and management studies. The authors undertook screening and data extraction in duplicate; it was not clear whether this was true for validity assessment, which meant that reviewer error and bias could not be ruled out. No formal tests of statistical heterogeneity were reported, but where heterogeneity was deemed to be present a narrative synthesis was appropriate. The authors acknowledged limitations with the included studies, such as their quality and heterogeneity in definitions of food allergy. The authors acknowledged that they did not formally evaluate for publication bias. There were few details reported on participants in the management studies. Only a small number of studies were included for some comparisons. Given the limitations with the available evidence, the authors' conclusions seem appropriate, but interpretation should take into account potential limitations with the review process

IMPLICATIONS OF THE REVIEW FOR PRACTICE AND RESEARCH: Practice: The authors stated that there was a need for standard criteria to define a food allergy and a set of evidence-based guidelines from which to make a diagnosis. Research: The authors stated that there was a need for greater rigour in the design, execution and reporting of food allergy studies. There was a need for more controlled studies that assessed elimination diets in patients with non-anaphylactic food allergy symptoms

Szajewska H, Horvath A. [Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases.](#) *Curr Med Res Opin* 2010;26(2):423-37.

Abstract: **OBJECTIVE:** Infants with a documented hereditary risk of atopy (i.e., an affected parent and/or sibling) who cannot be breastfed exclusively are recommended to receive a formula with confirmed reduced allergenicity, i.e., a partially or extensively hydrolyzed formula (pHF and eHF, respectively), as a means of preventing allergic reactions. The efficacy of each hydrolyzed formula for the prevention of allergic diseases should be established separately, as factors such as the protein source, hydrolysis method and degree of hydrolysis that often depend on the manufacturer contribute to differences among hydrolysates. The aim was to systematically review data on the efficacy of a partially hydrolyzed 100% whey formula (pHF) in reducing the risk of allergy in healthy infants at high risk for allergy. **METHODS:** The Cochrane Library, MEDLINE, EMBASE, and CINAHL databases were searched in September 2009 (from inception to September 2009) for randomized and quasi-randomized controlled trials (RCTs); additional references were obtained from reviewed articles. The company that manufactures the pHF used was contacted for unpublished data. **RESULTS:** The search yielded 84 citations. Fifteen RCTs were included, some of which had potential methodological limitations such as unclear or inadequate allocation concealment, no intention-to-treat analysis, and no true blinding. For primary outcomes, i.e., all allergic diseases and atopic eczema/atopic dermatitis, use of the pHF compared with standard formula (SF) was associated with reduced risks (incidence, cumulative incidence, period prevalence) that were statistically significant for most, albeit not all, time points. Comparison of groups

who received the pHF versus extensively hydrolyzed (eH) whey formula revealed no significant differences in outcomes except for reductions in the cumulative incidences of all allergic diseases at 0 to 36 months of age. Comparison of groups who received the pHF versus eH casein formula revealed no significant difference in outcomes between groups., CONCLUSIONS: The use of the pHF compared to SF is effective in allergy prevention in children at high risk for allergy at most time points. These results should be interpreted with caution due to a lack of methodological rigor in many trials. Reassuringly, the strongest evidence comes from a well-designed and conducted, independently funded RCT

Tang MLK, Lahtinen SJ, Boyle RJ. Probiotics and prebiotics: clinical effects in allergic disease. *Curr Opin Pediatr* 2010;22(5):626-34.

Abstract: PURPOSE OF REVIEW: This paper summarizes recent publications on probiotics and prebiotics in allergic disease. It focuses on clinical studies of prevention or treatment of allergic disease., RECENT FINDINGS: Studies suggest a role for certain probiotics (alone or with prebiotics) in the prevention of atopic eczema. Treatment during the prenatal period appears to be important for beneficial effects. The use of probiotics for the treatment of established allergic disease is less promising, despite some positive results. A Cochrane systematic review concluded that, when the results for the different probiotic strains used in clinical trials are pooled, probiotics are not effective for the treatment of eczema. There are fewer studies of prebiotics for the treatment or prevention of allergic disease, but data suggest that prebiotic-supplemented formulas may be effective for preventing eczema in infants at high risk of developing allergic disease when breast-feeding is not possible., SUMMARY: Allergic diseases continue to increase in prevalence worldwide, and primary prevention of allergic disease has proved an elusive goal. Probiotic bacteria represent the most promising intervention for primary prevention that has been studied to date, and definitive intervention studies should now be a research priority

Thompson RL, Miles LM, Lunn J, Devereux G, Dearman RJ, Strid J, et al. Peanut sensitisation and allergy: influence of early life exposure to peanuts. *Br J Nutr* 2010;103(9):1278-86.

Abstract: The aim of the present systematic review was to evaluate the influence of early life exposure (maternal and childhood) to peanuts and the subsequent development of sensitisation or allergy to peanuts during childhood. Studies were identified using electronic databases and bibliography searches. Studies that assessed the impact of non-avoidance compared with avoidance or reduced quantities of peanuts or peanut products on either sensitisation or allergy to peanuts, or both outcomes, were eligible. Six human studies were identified: two randomised controlled trials, two case-control studies and two cross-sectional studies. In addition, published animal and mechanistic studies, relevant to the question of whether early life exposure to peanuts affects the subsequent development of peanut sensitisation, were reviewed narratively. Overall, the evidence reviewed was heterogeneous, and was limited in quality, for example, through lack of adjustment for potentially confounding factors. The nature of the evidence has therefore hindered the development of definitive conclusions. The systematic review of human studies and narrative expert-led reviews of animal studies do not provide clear evidence to suggest that either maternal exposure, or early or delayed introduction of peanuts in the diets of children, has an impact upon subsequent development of sensitisation or allergy to peanuts. Results from some animal studies (and limited evidence from human subjects) suggest that the dose of peanuts is an important

mediator of peanut sensitisation and tolerance; low doses tend to lead to sensitisation and higher doses tend to lead to tolerance

van der Aa LB, Heymans HS, van Aalderen WM, Sprikkelman AB. Probiotics and prebiotics in atopic dermatitis: review of the theoretical background and clinical evidence. *Pediatr Allergy Immunol* 2010;21(2 Part 2):e355-e367.

Abstract: RECORD STATUS: This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn

AUTHOR'S OBJECTIVES: To examine the clinical evidence for using probiotics, prebiotics and synbiotics in the prevention and treatment of atopic dermatitis in children

SEARCHING: PubMed, EMBASE and The Cochrane Library were searched from inception to February 2008. Search terms were reported. Reference lists of retrieved papers were reviewed

VALIDITY ASSESSMENT: Quality of the included studies was assessed with Dutch Institute for Health Care Improvement (CBO) criteria, which graded studies as: A2 for good-quality RCTs and B for poorer quality RCTs. The authors did not state how each quality component was assessed. The authors did not state how many reviewers assessed quality of the included studies

DATA EXTRACTION: The effect of intervention on atopic dermatitis incidence was compared between intervention and control groups in a qualitative synthesis and with the Scoring Atopic Dermatitis (SCORAD) index for treatment studies. Odds ratio (OR) and hazards ratio (HR), with confidence intervals (CI), and incidence rate were calculated from change in atopic dermatitis incidence between pre- and post-intervention periods. The authors did not state how many reviewers extracted the data

RESULTS OF THE REVIEW: Eighteen studies were included: seven prevention (n=2,197) and 11 treatment (n=712) studies that met the inclusion criteria. Seven RCTs assessed prevention and 11 RCTs assessed treatment of atopic dermatitis, although the authors stated that 12 studies assessed treatment. Six of the seven studies that assessed prevention were level A2 and one was level B. Seven of the 11 treatment studies were level A2 evidence. Results on use of probiotics in prevention of atopic dermatitis were mixed. One study reported a 50% reduction in the incidence of atopic dermatitis compared to placebo and another study showed no reduction. One study showed that only one strain of probiotics reduced incidence of atopic dermatitis. Treatment of atopic dermatitis with probiotics showed conflicting results: four studies demonstrated reduction of SCORAD score and three studies showed no effect on atopic dermatitis, but did show a significantly modest SCORAD score with IgE-associated atopic dermatitis. The one double-blind RCT conducted so far showed that incidence of atopic dermatitis was significantly lower in prebiotics group than the placebo group (9.8% versus 23.1%). A large proportion (>20%) of the infants were lost to follow-up during the intervention period. Four studies reported no effect on the severity of atopic dermatitis in any group. The one study that investigated the use of synbiotics for the treatment of atopic dermatitis showed a significant improvement, but synbiotics did not appear to be superior to prebiotics alone. Two studies that assessed the effect of probiotics on food allergies as a secondary outcome did not find any difference in incidence

AUTHOR'S CONCLUSION: There was insufficient evidence in support of the use of probiotics, prebiotics or synbiotics for the prevention or treatment of atopic dermatitis in children in clinical practice

CRD COMMENTARY: This review addressed a clear research question. The search included appropriate electronic databases. No apparent attempts were made to retrieve unpublished studies, so some relevant studies might not have been included. No information about data extraction was provided and errors could not be ruled out. The lack of multiple

reviewers raised concerns about the potential for errors and bias. Risk of bias in the included studies could not be ruled out. Although potential sources of heterogeneity were explored qualitatively, this could not be addressed in the review. Not all of the included evidence was referred to in the synthesis. Methodological limitations in the included studies and the review process made the extent to which the authors' conclusions are reliable unclear

IMPLICATIONS OF THE REVIEW FOR PRACTICE AND RESEARCH: Practice: The authors did not state any implications for practice. Research: The authors stated that a large well-designed placebo controlled randomised trial with different probiotic strains was needed to draw definitive conclusions about prebiotics in the treatment and prevention of atopic dermatitis

Faktorer knyttet til barnets omgivelser.

Studiene omfatter påvirkning fra omgivelsene som forurensning og kvaliteten på innemiljøet i boligen, til passiv røyking og kjæledyr. Oversiktene er sortert alfabetisk etter førsteforfatter.

Anderson HR, Ruggles R, Pandey KD, Kapetanakis V, Brunekreef B, Lai CKW, et al. Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children: Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC). *Occup Environ Med* 2010;67(5):293-300.

Abstract: OBJECTIVES: To investigate the effect of ambient particulate matter on variation in childhood prevalence of asthma, rhinoconjunctivitis and eczema., METHODS: Prevalences of asthma, rhinoconjunctivitis and eczema obtained in Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC) were matched with city-level estimates of residential PM(10) obtained from a World Bank model. Associations were investigated using binomial regression adjusting for GNP per capita and for clustering within country. For countries with more than one centre, a two stage meta-analysis was carried out. The results were compared with a meta-analysis of published multi-centre studies., RESULTS: Annual concentrations of PM(10) at city level were obtained for 105 ISAAC centres in 51 countries. After controlling for GNP per capita, there was a weak negative association between PM(10) and various outcomes. For severe wheeze in 13-14-year-olds, the OR for a 10 microg/m³ increase in PM(10) was 0.92 (95% CI 0.84 to 1.00). In 24 countries with more than one centre, most summary estimates for within-country associations were weakly positive. For severe wheeze in 13-14-year-olds, the summary OR for a 10 microg/m³ increase in PM(10) was 1.01 (0.92 to 1.10). This result was close to a summary OR of 0.99 (0.91 to 1.06) obtained from published multi-centre studies., CONCLUSIONS: Modelled estimates of particulate matter at city level are imprecise and incomplete estimates of personal exposure to ambient air pollutants. Nevertheless, our results together with those of previous multi-centre studies, suggest that urban background PM(10) has little or no association with the prevalence of childhood asthma, rhinoconjunctivitis or eczema either within or between countries

Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;129(4):735-44.

Abstract: OBJECTIVES: Exposure to passive smoke is a common and avoidable risk factor for wheeze and asthma in children. Substantial growth in the prospective cohort study evidence base provides an opportunity to generate new and more detailed estimates of the magnitude of the effect. A systematic review and meta-analysis was conducted to provide estimates of the prospective effect of smoking by parents or household members on the risk of wheeze and asthma at different stages of childhood., METHODS: We systematically searched Medline, Embase, and conference abstracts to identify cohort studies of the incidence of asthma or wheeze in relation to exposure to prenatal or postnatal maternal, paternal, or household smoking in subjects aged up to 18 years old. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated by using random effects model., RESULTS: We identified 79 prospective studies. Exposure to pre- or postnatal passive smoke exposure was associated with a 30% to 70% increased risk of incident wheezing (strongest effect from postnatal maternal smoking on wheeze in children aged ≤ 2 years, OR = 1.70, 95% CI = 1.24-2.35, 4 studies) and a 21% to 85% increase in incident asthma (strongest effect from prenatal maternal smoking on asthma in children aged ≤ 2 years, OR = 1.85, 95% CI = 1.35-2.53, 5 studies)., CONCLUSIONS: Building upon previous findings, exposure to passive smoking increases the incidence of wheeze and asthma in children and young people by at least 20%. Preventing parental smoking is crucially important to the prevention of asthma

Chen CM, Tischer C, Schnappinger M, Heinrich J. The role of cats and dogs in asthma and allergy--a systematic review. *Int J Hyg Environ Health* 2010;213(1):1-31.

Abstract: Studies have reported contradictory effects of cat and dog exposure on allergy, resulting in inconsistent recommendations on animal avoidance. We conducted a systematic review of observational studies published in English from 2000 to January 2009. It shows in this review that the reported exposure-response relationships are contradictory. A total of 17 and 13 birth cohort studies on cat and dog exposure, respectively, are included in the review. Most of the birth cohort studies found that cat or dog exposure in early life had no effect on the development of asthma or wheezing symptoms and dog exposure during infancy was found to protect children from developing sensitization against aeroallergens. A total of 7 and 6 prospective studies in school-age children or adults on cat and dog exposure, respectively, are included in this review and most of these studies suggested an inverse association between cat exposure and asthma and wheezing symptoms. As for cross-sectional studies, 26 and 21 studies on cat and dog exposure, respectively, are included in this review, which cover a broad range of age groups and geographical areas, and reported inconsistent results. The evidence summarised in this systematic review needs to be interpreted with caution, the inconsistent study results may be due to study design, exposure assessment, and avoidance measure. The exposure-response relationships may also alter in geographical areas where the community prevalence of cats and dogs are significantly different. However, as the evidence of the effects of pet keeping on subsequent development of asthma or allergic diseases presented in this review are not overwhelmingly strong, the decision of whether to keep a cat or a dog in the family should be based on arguments other than the concern of developing asthma and allergy.

Gasana J, Dillikar D, Mendy A, Forno E, Ramos VE. Motor vehicle air pollution and asthma in children: A meta-analysis. *Environ Res* 2012; Jun 6. [Epub ahead of print]

Abstract: BACKGROUND: Asthma affects more than 17 million people in the United States; 1/3 of these are children. Children are particularly vulnerable to airborne pollution because of their narrower airways and because they generally breathe more air per pound of body weight than adults, increasing their exposure to air pollutants. However, the results from previous studies on the association between motor vehicle emissions and the development of childhood wheeze and asthma are conflicting. Therefore, we conducted a meta-analysis to clarify their potential relationship. METHODS: MEDLINE, HighWire, and The Cochrane Library databases were searched for relevant studies. Adjusted odds ratio (OR) with corresponding 95% confidence interval (CI) for the association between traffic air pollutants and wheeze or asthma were retrieved from individual studies and pooled to generate summary effect estimates (meta-OR) in STATA 11.1. RESULTS: Nineteen studies were included in the meta-analysis. Exposure to nitrogen dioxide (meta-OR: 1.05, 95% CI: 1.00-1.11), nitrous oxide (meta-OR: 1.02, 95% CI: 1.00-1.04), and carbon monoxide (meta-OR: 1.06, 95% CI: 1.01-1.12) were positively associated with a higher prevalence of childhood asthma. Exposure to sulfur dioxide (meta-OR: 1.04, 95% CI: 1.01-1.07) was positively associated with a higher prevalence of wheeze in children. Exposure to nitrogen dioxide was positively associated with a higher incidence of childhood asthma (meta-OR: 1.14, 95% CI: 1.06-1.24), and exposures to particulate matter was positively associated with a higher incidence of wheeze in children (meta-OR: 1.05, 95% CI: 1.04-1.07). CONCLUSIONS: Living or attending schools near high traffic density roads exposes children to higher levels of motor vehicle air pollutants, and increases the incidence and prevalence of childhood asthma and wheeze

Genuneit J. Exposure to farming environments in childhood and asthma and wheeze in rural populations: a systematic review with meta-analysis. *Pediatr Allergy Immunol* 2012; May 25. doi: 10.1111/j.1399-3038.2012.01312.x. [Epub ahead of print]

ABSTRACT: Asthma is a chronic respiratory disorder that has become substantially more common over the past decades. One environmental factor for which particularly strong associations with asthma and allergic diseases have been described is exposure to farming environments in childhood. The aim of this systematic review was to update and extend existing narrative reviews, test for heterogeneity of effect across studies, and conduct a meta-analysis to report a summary effect measure. Published relevant literature was searched through PubMed including all articles added to PubMed before September 1, 2011. Articles were included if they reported an epidemiological study on the exposure to a farming environment in childhood and subsequent wheeze or asthma. Heterogeneity of effect measures across studies was evaluated using Cochran's Q and I(2). Random-effects meta-analysis was performed to summarize effect measures for various outcome definitions. In total, 357 retrieved abstracts revealed 52 original articles from 39 studies with data considered for the meta-analysis. Most studies were conducted among children or on childhood onset of disease. Most data were published on doctor-diagnosed asthma or current wheeze. The meta-analysis showed substantial heterogeneity across studies with similar outcome definitions. Nonetheless, the combined effects were statistically significant and showed an approximate 25% lower asthma prevalence among exposed subjects compared with unexposed subjects. The protective 'farm-effect' on asthma was reported in numerous studies. Its underlying factors ought to be studied, and promising efforts have been already made. However, the heterogeneity of the effect across studies should also be investigated because whatever causes it is a potential threat to valid synthesis of evidence and to the detection of specific protective factors

Kabir Z, Alpert HR, Goodman PG, Haw S, Behm I, Connolly GN, et al. Effect of smoke-free home and workplace policies on second-hand smoke exposure levels in children: an evidence summary. *Pediatric Health* 2010;4(4):391-403.

Abstract: RECORD STATUS: This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn

AUTHOR'S OBJECTIVES: To assess the effect of smoke-free home and workplace policies on second-hand smoke exposure levels in children

SEARCHING: PubMed, EMBASE and Cochrane Tobacco Addiction Group Specialised Register were searched from January 2000 to April 2010 for studies published in English. Search terms were reported. The Journal of Tobacco Control and relevant grey literature were also searched

VALIDITY ASSESSMENT: Formal quality assessment was not performed

DATA EXTRACTION: Data were extracted on percentage of participants experiencing an event or odd ratios with 95% confidence intervals. The authors did not state how many reviewers performed data extraction

RESULTS OF THE REVIEW: Nineteen studies were included in the review. The total number of participants was not reported. Voluntary household smoking restrictions were associated with a reduction in childhood second-hand smoke exposure (ranging between 20% and 50% reductions). Mandated comprehensive workplace and enclosed public smoke-free policies led to a benefit in participants' health outcomes, including a decrease in preterm birth risks and a reduction in emergency hospital visits due to asthma

AUTHOR'S CONCLUSION: The evidence suggested that any reductions in second-hand smoke exposure levels in public settings would ultimately lead to improvements in the general health of children in private settings but smoke-free home policies would have additional benefits

CRD COMMENTARY: This review's inclusion criteria were clear. Relevant databases were searched. Efforts were made to find both published and unpublished studies, which minimised the potential for publication bias. It appeared that this review mainly included studies in English, which may have increased the risk of language bias. It was unclear whether sufficient attempts were made to minimise reviewers' errors and biases in the review process. The authors discussed some aspects of study quality such as study power, but a formal quality assessment was not performed. Most of the included studies were observational studies, which were susceptible to bias. Given the diversity of included studies in relation to study design and outcomes, a narrative synthesis was appropriately employed. Given the limited methodological rigour of included studies, the authors' conclusions should be interpreted with caution

IMPLICATIONS OF THE REVIEW FOR PRACTICE AND RESEARCH: Practice: The authors stated that childhood second-hand smoke exposure in private settings should be considered an intervention priority in paediatric and public health settings. Health professionals and other key stakeholders need appropriate training relating to the issues on smoking in the home and how to address these issues. Research: The authors stated that further research was required to investigate interventions on reducing second-hand smoke exposure levels in children and develop a more robust evidence base to inform effective actions on this issue. Future studies (with a long-term follow-up) should be conducted with an appropriate representative sample and personalised second-hand smoke exposure measurements across different population settings. Studies from low-income countries were required. Further studies to evaluate additional paediatric outcomes strongly associated with sudden infant death syndrome and otitis media were also required

Latza U, Gerdes S, Baur X. Effects of nitrogen dioxide on human health: systematic review of experimental and epidemiological studies conducted between 2002 and 2006.

Int J Hyg Environ Health 2009;212(3):271-87.

Abstract: In order to assess health effects in humans caused by environmental nitrogen dioxide (NO₂) a systematic review of studies in humans was conducted. MEDLINE database was searched for epidemiological studies and experiments on adverse effects of NO₂ published between 2002 and 2006. The evidence with regard to NO₂ exposure limits was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) grading system and the modified three star system. Of the 214 articles retrieved 112 fulfilled the inclusion criteria. There was limited evidence that short-term exposure to a 1-h mean value below 200 microg NO₂/m³ is associated with adverse health effects provided by only one study on mortality in patients with severe asthma (*2+). The effect remained after adjusting for other air pollutants. There was moderate evidence that short-term exposure below a 24-h mean value of 50 microg NO₂/m³ at monitor stations increases hospital admissions and mortality (**2+). Evidence was also moderate when the search was restricted to susceptible populations (children, adolescents, elderly, and asthmatics). There was moderate evidence that long-term exposure to an annual mean below 40 microg NO₂/m³ was associated with adverse health effects (respiratory symptoms/diseases, hospital admissions, mortality, and otitis media) provided by generally consistent findings in five well-conducted cohort and case-control studies with some shortcomings in the study quality (**2+). Evidence was also moderate when the search was restricted to studies in susceptible populations (children and adolescents) and for the combination with other air pollutants. The most frequent reasons for decreased study quality were potential misclassification of exposure and selection bias. None of the high-quality observational studies evaluated was informative for the key questions due to the choice of the dose parameter (e.g., 1-week mean) and exposure levels above the limit values. Inclusion of study designs unlisted in the SIGN grading system did not bring additional evidence regarding exposures below the current air quality limit values for NO₂. As several recent studies reported adverse health effects below the current exposure limits for NO₂ particularly among susceptible populations regarding long-term exposure further research is needed. Apart from high-quality epidemiological studies on causality and the interaction of NO₂ with other air pollutants there is a need for double-blinded randomized crossover studies among susceptible populations for further evaluation of the short-term exposure limits

Lodge CJ, Allen KJ, Lowe AJ, Hill DJ, Hosking CS, Abramson MJ, et al. Perinatal cat and dog exposure and the risk of asthma and allergy in the urban environment: a systematic review of longitudinal studies. Clin Dev Immunol 2012;2012:176484.

Abstract: BACKGROUND: The literature is contradictory concerning pet exposure and the risk of development of asthma and other allergic diseases. Using longitudinal studies, we aimed to systematically review the impact of pet ownership in the critical perinatal period as a risk factor for allergies in childhood., METHODS: Medline database was searched for urban cohort studies with perinatal exposure to cats and/or dogs and subsequent asthma or allergic disease., RESULTS: Nine articles, comprising 6498 participants, met inclusion criteria. Six found a reduction in allergic disease associated with perinatal exposure to dogs or, cats or dogs. One study found no association. Two found increased risk only in high-risk groups., CONCLUSION: Longitudinal studies in urban populations suggest that perinatal pets, especially dogs, may reduce the development of allergic disease in those without a family history of allergy. Other unmeasured factors such as pet-keeping choices in allergic families may be confounding the association seen in these high-risk families, and further study is required

McGwin G, Lienert J, Kennedy JI. Formaldehyde exposure and asthma in children: a systematic review. Environ Health Perspect 2010;118(3):313-7.

Abstract: OBJECTIVE: Despite multiple published studies regarding the association between formaldehyde exposure and childhood asthma, a consistent association has not been identified. Here we report the results of a systematic review of published literature in order to provide a more comprehensive picture of this relationship., DATA SOURCES: After a comprehensive literature search, we identified seven peer-reviewed studies providing quantitative results regarding the association between formaldehyde exposure and asthma in children. Studies were heterogeneous with respect to the definition of asthma (e.g., self-report, physician diagnosis). Most of the studies were cross-sectional., DATA EXTRACTION: For each study, an odds ratio (OR) and 95% confidence interval (CI) for asthma were either abstracted from published results or calculated based on the data provided. Characteristics regarding the study design and population were also abstracted., DATA SYNTHESIS: We used fixed- and random-effects models to calculate pooled ORs and 95% CIs; measures of heterogeneity were also calculated. A fixed-effects model produced an OR of 1.03 (95% CI, 1.021.04), and random effects model produced an OR of 1.17 (95% CI, 1.011.36), both reflecting an increase of 10 microg/m³ of formaldehyde. Both the Q and I² statistics indicated a moderate amount of heterogeneity., CONCLUSIONS: Results indicate a significant positive association between formaldehyde exposure and childhood asthma. Given the largely cross-sectional nature of the studies underlying this meta-analysis, further well-designed prospective epidemiologic studies are needed

McGwin GJ, Lienert J, Kennedy JIJ. Formaldehyde exposure and asthma in children: a systematic review. Cienc saude colet 2011;16(9):3845-52.

Abstract: Despite multiple published studies regarding the association between formaldehyde exposure and childhood asthma, a consistent association has not been identified. Here we report the results of a systematic review of published literature in order to provide a more comprehensive picture of this relationship. After a literature search, we identified seven studies providing quantitative results regarding the association between formaldehyde exposure and asthma in children. Studies were heterogeneous with respect to the definition of asthma. For each study, an odds ratio (OR) and 95% confidence interval (CI) for asthma were abstracted from published results or calculated based on the data provided. We used fixed- and random-effects models to calculate pooled ORs and 95% CIs; measures of heterogeneity were also calculated. A fixed-effects model produced an OR of 1.03 (95% CI, 1.021.04), and random effects model produced an OR of 1.17 (95% CI, 1.011.36), both reflecting an increase of 10 mg/m³ of formaldehyde. Both the Q and I² statistics indicated a moderate amount of heterogeneity. Results indicate a positive association between formaldehyde exposure and childhood asthma. Given the largely cross-sectional nature of the studies underlying this meta-analysis, further well-designed prospective epidemiologic studies are needed

Po JYT, FitzGerald JM, Carlsten C. Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax 2011;66(3):232-9.

Abstract: BACKGROUND: Numerous studies with varying associations between domestic use of solid biomass fuels (wood, dung, crop residue, charcoal) and respiratory diseases have been reported., OBJECTIVE: To present the current data systematically associating use of biomass fuels with respiratory outcomes in rural women and children.,

METHODS: Systematic searches were conducted in 13 electronic databases. Data were abstracted from original articles that satisfied selection criteria for meta-analyses. Publication bias and heterogeneity of samples were tested. Studies with common diagnoses were analysed using random-effect models., **RESULTS:** A total of 2717 studies were identified. Fifty-one studies were selected for data extraction and 25 studies were suitable for meta-analysis. The overall pooled ORs indicate significant associations with acute respiratory infection in children (OR 3.53, 95% CI 1.94 to 6.43), chronic bronchitis in women (OR 2.52, 95% CI 1.88 to 3.38) and chronic obstructive pulmonary disease in women (OR 2.40, 95% CI 1.47 to 3.93). In contrast, no significant association with asthma in children or women was noted., **CONCLUSION:** Biomass fuel exposure is associated with diverse respiratory diseases in rural populations. Concerted efforts in improving stove design and lowering exposure to smoke emission may reduce respiratory disease associated with biomass fuel exposure

Roosli M, Hug K. Wireless communication fields and non-specific symptoms of ill health: a literature review. Wien Med Wochenschr 2011;161(9-10):240-50.

Abstract: This is an update of a previous systematic review on the association between radiofrequency electromagnetic field (RF-EMF) exposure and health-related quality of life that included studies published before August 2007 [1]. Since then, nine randomized trials addressed short-term exposures from close-to-body RF-EMF sources such as mobile phones, and two observational studies investigated the effects of mobile phone use on health-related quality of life. Six randomized trials addressed short-term far-field exposure arising, for instance, from mobile phone base stations, and eight studies evaluated the effects of environmental far-field RF-EMF exposure. In most of the randomized trials, no exposure-response association was observed. The sporadically reported associations did not show a consistent pattern regarding the type of symptoms or the direction of the effects (increase/decrease). Similarly, most of the recent observational studies did not show associations between RF-EMF exposure and non-specific symptoms. However, the exposure gradients were small and possible exposure misclassification is a limitation of these studies. Longitudinal studies as well as studies in children and adolescents are scarce. In summary, recent research did not indicate health-related quality of life to be affected by RF-EMF exposure in our everyday environment. Furthermore, none of the studies showed that individuals with self-reported electromagnetic hypersensitivity (EHS) were more susceptible to RF-EMF than the rest of the population. Nevertheless, the rapid technological development and anticipated increase in exposure levels warrant the conduct of further longitudinal studies. Due to the widespread use of wireless communication technologies potential adverse health effects would have major public health consequences

Sauni R, Uitti J, Jauhiainen M, Kreiss K, Sigsgaard T, Verbeek JH. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. Cochrane Database Syst Rev 2011;9:CD007897.

Abstract: **BACKGROUND:** Dampness and mould in buildings have been associated with adverse respiratory symptoms, asthma and respiratory infections of inhabitants. Moisture damage is a very common problem in private houses, workplaces and public buildings such as schools., **OBJECTIVES:** To determine the effectiveness of remediating buildings damaged by dampness and mould in order to reduce or prevent respiratory tract symptoms, infections and symptoms of asthma., **SEARCH STRATEGY:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 2), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1951 to June week 1, 2011), EMBASE (1974 to June 2011), CINAHL

(1982 to June 2011), Science Citation Index (1973 to June 2011), Biosis Previews (1989 to June 2011), NIOSHTIC (1930 to November 2010) and CISDOC (1974 to November 2010)., SELECTION CRITERIA: Randomised controlled trials (RCTs), cluster-RCTs (cRCTs), interrupted time series studies and controlled before-after (CBA) studies of the effects of remediating dampness and mould in a building on respiratory symptoms, infections and asthma., DATA COLLECTION AND ANALYSIS: Two authors independently extracted data and assessed the risk of bias in the included studies., MAIN RESULTS: We included eight studies (6538 participants); two RCTs (294 participants), one cRCT (4407 participants) and five CBA studies (1837 participants). The interventions varied from thorough renovation to cleaning only. We found moderate-quality evidence in adults that repairing houses decreased asthma-related symptoms (among others, wheezing (odds ratio (OR) 0.64; 95% confidence interval (CI) 0.55 to 0.75) and respiratory infections (among others, rhinitis (OR 0.57; 95% CI 0.49 to 0.66)). For children, we found moderate-quality evidence that the number of acute care visits (among others mean difference (MD) -0.45; 95% CI -0.76 to -0.14)) decreased in the group receiving thorough remediation. One CBA study showed very low-quality evidence that after repairing a mould-damaged office building, asthma-related and other respiratory symptoms decreased. For children and staff in schools, there was very low-quality evidence that asthma-related and other respiratory symptoms in mould-damaged schools were similar to those of children and staff in non-damaged schools, both before and after intervention. For children, respiratory infections might have decreased after the intervention., AUTHORS' CONCLUSIONS: We found moderate to very low-quality evidence that repairing mould-damaged houses and offices decreases asthma-related symptoms and respiratory infections compared to no intervention in adults. There is very low-quality evidence that although repairing schools did not significantly change respiratory symptoms in staff or children, pupils' visits to physicians due to a common cold were less frequent after remediation of the school. Better research, preferably with a cRCT design and with more validated outcome measures, is needed

Schmitt J, Apfelbacher CJ, Flohr C. Eczema. Clin Evid (Online) 2011.

Abstract: INTRODUCTION: Eczema, as defined by the World Allergy Organization (WAO) revised nomenclature in 2003, affects 15% to 20% of school children and 2% to 5% of adults worldwide. About 50% of people with eczema demonstrate atopy, with specific immunoglobulin E responses to allergens. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of topical medical treatments, and dietary interventions in adults and children with established eczema? What are the effects of breastfeeding, reducing allergens, or dietary interventions for primary prevention of eczema in predisposed infants? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2009 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA)., RESULTS: We found 54 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions., CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: breastfeeding, controlling house dust mites, corticosteroids, dietary exclusion of eggs or cow's milk, elementary diets, emollients, essential fatty oils, few-foods diet, multivitamins, pimecrolimus, probiotics, pyridoxine, reducing maternal dietary allergens, tacrolimus, vitamin E, and zinc supplements

Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, Spuls PI. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. Br J Dermatol 2010;162(5):964-73.

Abstract: BACKGROUND: Eczema affects approximately 10% of all schoolchildren in the western world and has shown an increase over the past decades in 'developing' countries. Numerous factors have been suggested that might contribute to the increasing prevalence of eczema. A plausible explanation is the role of environmental factors. As part of the 'hygiene hypothesis' it has been thought that eczema is more common in urban than in rural communities, but such a notion has never been assessed systematically., OBJECTIVE: Our aim was to assess whether there is a rural/urban gradient for the prevalence of eczema and, if so, to what extent., METHODS: All data sources were identified through a search in MEDLINE and EMBASE. All primary studies comparing the prevalence rate of eczema between urban and rural populations were assessed for eligibility. Included articles were reviewed for methodological quality and a relative risk was calculated to indicate the risk of eczema in urban over rural areas. Results Twenty-six articles were included for analysis. Nineteen showed a higher risk for eczema in an urbanized area, of which 11 were significant. Six studies showed a lower risk of eczema in an urbanized area, of which one was statistically significant. One study had a relative risk of 1.00., RESULTS: were more homogeneous among studies of good methodological quality. A pooled relative risk could have been calculated but was not because of heterogeneity., CONCLUSION: There is some evidence of a higher risk for eczema in urban compared with rural areas, suggesting that place of residence may have a role in the pathogenesis of eczema. Future reviews on environmental circumstances should be carried out to reveal the factors associated with a higher prevalence of eczema in urban areas and the association with other allergic diseases

Simons E, To T, Dell S. The population attributable fraction of asthma among Canadian children. Can J Public Health 2011;102(1):35-41.

Abstract: OBJECTIVE: We calculated the population attributable fraction (PAF) of Canadian childhood asthma due to modifiable environmental exposures, in order to estimate their relative contributions to asthma development based on the current literature., METHODS: We conducted a systematic review to determine Canadian childhood asthma incidence, Canadian prevalence of exposure to airborne pollutants and indoor allergens, and international estimates of the risk of developing physician-diagnosed asthma (PDA) associated with each exposure. Combining risk estimates by meta-analysis where possible, PAF was calculated by the formula: $PAF = \text{Attributable risk} \times \text{Exposure prevalence} \times 100\% / \text{Asthma incidence}$., SYNTHESIS: Age-specific Canadian childhood asthma incidence ranged from 2.8%-6.9%. Canadian exposure prevalences were: PM10 16%, PM2.5 7.1%, NO2 25%, environmental tobacco smoke (ETS) 9.0%, cat 22%, dog 12%, mouse 17%, cockroach 9.8%, dust mite 30%, moisture 14% and mould 33%. Relative risk estimates of PDA were: PM10 1.64, PM2.5 1.44, NO2 1.29, ETS 1.40, mouse 1.23, cockroach 1.96, and spanned 1.00 for cat, dog, dust mites, moisture and mould. PAF estimates for incident asthma among preschool children were: PM10 11%, PM2.5 1.6%, NO2 4.0%, ETS 2.9%, mouse 6.5% and cockroach 13%., CONCLUSIONS: This systematic review suggests contributions to childhood asthma development from exposure to particulates, NO2, ETS, mouse and cockroach. The associations appeared to be more complex for cat, dog and dust mite allergens and more variable for mould and moisture. Additional prospective, population-based studies of childhood asthma development with objectively-measured exposures are needed to further quantify these associations

Takenoue Y, Kaneko T, Miyamae T, Mori M, Yokota S. The influence of outdoor NO(2) exposure on asthma in childhood: a meta-analysis. *Pediatrics international : official journal of the Japan Pediatric Society* 2012; May 29. doi: 10.1111/j.1442-200X.2012.03674.x. [Epub ahead of print]

Abstract: Background: It has long been assumed that the development of childhood asthma is related to exposure to environmental chemicals. However, it has thus far not been possible to unequivocally establish this suspected relationship by individual studies. Moreover, studies of children have been scanty and unreliable due to the large diversity of research environments and subject cohorts. The current study was aimed at clarifying this relationship for one factor by means of a meta-analysis of studies investigating the influence of NO(2) exposure on symptomatology of childhood asthma. Methods: We searched two electronic databases (MEDLINE and EMBASE) for literature on relationships between environmental chemical exposure and development of childhood asthma using the MeSH terms nitrogen dioxide and asthma. We did this according to the MOOSE guidelines for meta-analyses of observational studies. Results: We retrieved 130 papers of which 12 met the selection criteria. These papers described observational studies from 7 countries. Study subjects were 97,932 ordinary children aged 0-18 years. Random model analysis revealed that the Odds Ratio (OR) for asthma development due to an increment of 10 ppb of NO(2) was 1.135 with a 95% CI of 1.031-1.251 (P=0.01), while the OR for wheezing symptoms was 1.052 with a 95% CI of 1.020-1.085 (P=0.001). It is therefore evident that NO(2) exposure does influence the development of asthma in ordinary children. Conclusions: Our meta-analysis indicated that exposure to NO(2) in the air significantly influenced the development of childhood asthma and symptoms of wheezing.

Tischer C, Chen CM, Heinrich J. Association between domestic mould and mould components, and asthma and allergy in children: a systematic review. *Eur Respir J* 2011;38(4):812-24.

Abstract: Critical reviews over the past 10 yrs have found increased respiratory and allergic health outcomes for children living in damp and mouldy environments. However, recent studies have suggested that early childhood exposure to specific mould components may actually protect children from developing allergy. We conducted a systematic review of observational studies published in English from January 1980 to July 2010. This review was conducted according to systematic guidelines for Meta-analyses of Observational Studies in Epidemiology (MOOSE). The literature was searched using a computerised bibliographic database, PubMed. In order to increase the quality of the reviewed studies, meta-analyses of the effects of visible mould exposure on allergic health outcomes were performed and we evaluated the findings according to the Bradford Hill criteria for evidence of causation. The literature search identified 1,398 peer-reviewed scientific publications, and 61 studies that fulfilled the inclusion criteria were included in this review. We observed increased risks of allergic respiratory health outcomes in children exposed to visible mould and mould spores. These findings were confirmed by the results of the meta-analysis and in line with the evaluation criteria according to Bradford Hill. Visible mould was positively associated with asthma (OR 1.49 (95% CI 1.28-1.72)), wheeze (OR 1.68 (95% CI 1.48-1.90)) and allergic rhinitis (OR 1.39 (95% CI 1.28-1.51)). However, there was a tendency of lower risk for allergic health outcomes in children exposed to mould-derived components such as (1,3)-beta-d-glucan and extracellular polysaccharides. These findings suggest that home environments with visible mould and mould spore exposure increase the risk of allergic respiratory health outcomes in children. However, further investigations are needed to examine the effects of exposure to mould-derived components as the current literature is inconclusive. In order to disentangle the different effects of overall microbial exposure on children's health, research should focus on specific microbial

markers in the home, in combination with new assessment techniques including molecular methods

Tischer CG, Hohmann C, Thiering E, Herbarth O, Muller A, Henderson J, et al. Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. *Allergy* 2011;66(12):1570-9.

Abstract: BACKGROUND: Several cross-sectional studies during the past 10 years have observed an increased risk of allergic outcomes for children living in damp or mouldy environments., OBJECTIVE: The objective of this study was to investigate whether reported mould or dampness exposure in early life is associated with the development of allergic disorders in children from eight European birth cohorts., METHODS: We analysed data from 31 742 children from eight ongoing European birth cohorts. Exposure to mould and allergic health outcomes were assessed by parental questionnaires at different time points. Meta-analyses with fixed- and random-effect models were applied. The number of the studies included in each analysis varied based on the outcome data available for each cohort., RESULTS: Exposure to visible mould and/or dampness during first 2 years of life was associated with an increased risk of developing asthma: there was a significant association with early asthma symptoms in meta-analyses of four cohorts [0-2 years: adjusted odds ratios (aOR), 1.39 (95% CI, 1.05-1.84)] and with asthma later in childhood in six cohorts [6-8 years: aOR, 1.09 (95% CI, 0.90-1.32) and 3-10 years: aOR, 1.10 (95% CI, 0.90-1.34)]. A statistically significant association was observed in six cohorts with symptoms of allergic rhinitis at school age [6-8 years: aOR, 1.12 (1.02-1.23)] and at any time point between 3 and 10 years [aOR, 1.18 (1.09-1.28)]., CONCLUSION: These findings suggest that a mouldy home environment in early life is associated with an increased risk of asthma particularly in young children and allergic rhinitis symptoms in school-age children.

Treyster Z, Gitterman B. Second hand smoke exposure in children: environmental factors, physiological effects, and interventions within pediatrics. *Rev Environ Health* 2011;26(3):187-95.

Abstract: BACKGROUND: Second hand smoke (SHS) exposure has long been correlated with many adverse disease processes, particularly in children. For children growing up with socioeconomic disadvantages and increased exposure to SHS, exposure can have far-reaching consequences., OBJECTIVE: The purpose of this review was to examine the literature assessing the effects of SHS exposure in children, as well as the perspectives of both parents and providers regarding current practices in cessation counseling. The review also sought out recommendations on ways to increase the influence of pediatricians on parental smoking., STUDY GROUP: Children under the age of 18 years., METHODS: PubMed and MEDLINE were searched systematically. A narrative approach was used because the studies differed in methods and data., RESULTS: The studies showed correlations between SHS exposure and sudden infant death syndrome (SIDS), asthma, altered respiratory function, infection, cardiovascular effects, behavior problems, sleep difficulties, increased cancer risk, and a higher likelihood of smoking initiation. Questionnaires of both parents and pediatricians showed that pediatricians are not consistently carrying out the recommended smoking cessation interventions, with lack of training as a primary barrier. Nevertheless, interventions targeting improved cessation training for both residents and practicing pediatricians have been studied and show promising results., CONCLUSIONS: SHS exposure has many detrimental effects on children's health, particularly for those in low socioeconomic circumstances, for which factors in the built environment accentuated a higher baseline risk. By counseling parents, expanding residency education, and continuing advocacy work, pedia-

tricians can have a significant positive impact on children's health as related to SHS exposure

Weinmayr G, Romeo E, De Sario M, Weiland SK, Forastiere F. Short-term effects of PM10 and NO2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. Environ Health Perspect 2010;118(4):449-57.

Abstract: OBJECTIVE: Our goal was to quantify the short-term effects of particulate matter with aerodynamic diameter ≤ 10 microm (PM10) and nitrogen dioxide (NO2) on respiratory health of asthmatic children from published panel studies, and to investigate the influence of study and population characteristics as effect modifiers., DATA EXTRACTION: After a systematic literature review, we extracted quantitative estimates of the association of PM10 and/or NO2 with respiratory symptoms and peak expiratory flow (PEF). Combined effect estimates for an increase of 10 microg/m³ were calculated by random effects meta-analysis for all studies and for different strata defined by study characteristics. The effect of publication bias was investigated with Egger's and Begg's tests and "trim-and-fill" analyses., DATA SYNTHESIS: We identified 36 studies; 14 were part of the European Pollution Effects on Asthmatic Children in Europe (PEACE) study. Adverse associations of PM10 with asthma symptoms were statistically significant [odds ratio (OR) = 1.028; 95% confidence interval (CI), 1.006-1.051]. There were also associations, although not statistically significant, of PM10 with cough (OR = 1.012; 95% CI, 0.997-1.026) and on PEF (decrease of -0.082 L/min; 95% CI, -0.214 to 0.050). NO2 had statistically significant associations with asthma symptoms in the overall analysis considering all possible lags (OR = 1.031; 95% CI, 1.001-1.062), but not when we evaluated only the 0-1 lag. We found no publication bias, although it appeared when excluding the PEACE studies. When we applied the trim-and-fill method to the data set without the PEACE studies, the results were similar to the overall estimates from all studies. There was an indication for stronger PM10 associations for studies conducted in summer, outside of Europe, with longer lags, and in locations with higher NO2 concentrations., CONCLUSIONS: We found clear evidence of effects of PM10 on the occurrence of asthma symptom episodes, and to a lesser extent on cough and PEF. The results for NO2 are more difficult to interpret because they depend on the lag times examined. There was an indication of effect modification by several study conditions

Xu Z, Etzel RA, Su H, Huang C, Guo Y, Tong S. Impact of ambient temperature on children's health: A systematic review. Environ Res 2012; Jul 23. [Epub ahead of print]

Abstract: BACKGROUND: A genome-wide association study identified ORM1-like 3 (orosomucoid 1-like 3, ORMDL3) as an asthma candidate gene. Single nucleotide polymorphisms (SNPs) in the region including ORMDL3 on chromosome 17q21 were related to childhood asthma risk and ORMDL3 expression levels in Europeans., OBJECTIVE: We examined whether polymorphisms in ORMDL3 and the adjacent gasdermin-like (GSDML) gene associated with asthma in the genome-wide association study are related to childhood asthma and atopy in a Mexico City population., METHODS: We genotyped rs4378650 in ORMDL3 and rs7216389 in GSDML in 615 nuclear families consisting of asthmatic children aged 4-17 years and their parents. Atopy was determined by skin prick tests to 25 aeroallergens., RESULTS: Individuals carrying the C allele of rs4378650 or the T allele of rs7216389 had increased risk of asthma [relative risk (RR) = 1.73, 95% confidence interval (CI) 1.19-2.53, P = 0.003 for one or two copies of rs4378650 C, and RR = 1.64, 95% CI 1.12-2.38, P = 0.009 for one or two copies of rs7216389 T]. Linkage disequilibrium between the two SNPs was high ($r^2 = 0.92$).

Neither of the SNPs was associated with the degree of atopy. A meta-analysis of five published studies on rs7216389 in nine populations gave an odds ratio for asthma of 1.44 (95% CI, 1.35-1.54, $P < 0.00001$). CONCLUSIONS: Our results and the meta-analysis provide evidence to confirm the finding from a recent genome-wide association study that polymorphisms in ORMDL3 and the adjacent GSDML may contribute to childhood asthma

Vedlegg

Søkestrategier

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	Asthma/	97734
2	Hypersensitivity/	35046
3	(asthma* or hypersensitiv* or hyper-sensitiv* or allerg*).tw.	255466
4	(food adj3 intoleran*).tw.	878
5	or/1-4	279746
6	child/ or child, preschool/ or infant/ or infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, postmature/ or infant, premature/	1888408
7	(child* or infant* or toddler* or baby or babies or newborn*).tw.	1184129
8	or/6-7	2181047
9	5 and 8	60902
10	limit 9 to "reviews (maximizes specificity)"	848
11	limit 10 to yr="2009 -Current"	301

CRD – 2012-08-01

Line	Search	Hits
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#1	((asthma* or hypersensitiv* or hyper-sensitiv* or allerg* or (food NEAR3 intoleran*)) and (child* or infant* or toddler* or baby or babies or newborn*)) IN DARE, HTA FROM 2009 TO 2012	142
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PubMed – 2012-08-02

Search	Query	Items found
#13	Search (((#1) AND #2) AND #11) AND #12	21
#12	Search publisher[sb]	419962
#11	Search (#4) OR #10	1868359
#10	Search meta analysis[Publication Type] OR meta analysis[Title/Abstract] OR meta analysis[MeSH Terms] OR review[Publication Type] OR search*[Title/Abstract]	1859346
#4	Search MEDLINE[Title/Abstract] OR (systematic[Title/Abstract] AND review[Title/Abstract]) OR meta analysis[Publication Type]	96401
#2	Search (child* or infant* or toddler* or baby or babies or newborn*)	2316835
#1	Search (asthma* or hypersensitiv* or hyper-sensitiv* or allerg* or food intoleran*)	307291

Cochrane reviews – 2012-08-01

ID	Search	Hits
#1	(asthma* or hypersensitiv* or hyper-sensitiv* or allerg* or (food NEAR/3 intoleran*)):ti,ab,kw and (child* or infant* or toddler* or baby or babies or newborn*):ti,ab,kw, from 2009 to 2012 in Cochrane Reviews	150