Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis

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EDITORIAL
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ABSTRACT

Objective To investigate whether filaggrin gene defects, present in up to one in 10 western Europeans and North Americans, increase the risk of developing allergic sensitisation and allergic disorders.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, ISI Science Citation Index, BIOSIS, ISI Web of Knowledge, UK National Research Register, clinical trials.gov, the Index to Theses and Digital dissertations, and grey literature using OpenSIGLE.

Study selection Genetic epidemiological studies (family, case-control) of the association between filaggrin gene defects and allergic sensitisation or allergic disorders.

Data extraction Atopic eczema or dermatitis, food allergy, asthma, allergic rhinitis, and anaphylaxis, along with relevant immunological variables relating to the risk of allergic sensitisation as assessed by either positive skin prick testing or increased levels of allergen specific IgE.

Data synthesis 24 studies were included. The odds of developing allergic sensitisation was 1.91 (95% confidence interval 1.44 to 2.54) in the family studies and 1.57 (1.20 to 2.07) in the case-control studies. The odds of developing atopic eczema was 1.99 (1.72 to 2.31) in the family studies and 4.78 (3.31 to 6.92) in the case-control studies. Three studies investigated the association between filaggrin gene mutations and allergic rhinitis in people without atopic eczema: overall odds ratio 1.78 (1.16 to 2.73). The four studies that investigated the association between filaggrin gene mutations and allergic rhinitis in people with atopic eczema reported a significant association: pooled odds ratio from case-control studies 2.84 (2.08 to 3.88). An overall odds ratio for the association between filaggrin gene mutations and asthma in people with atopic eczema was 2.79 (1.77 to 4.41) in case-control studies and 2.30 (1.66 to 3.18) in family studies. None of the studies that investigated filaggrin gene mutations and asthma in people without atopic eczema reported a significant association; overall odds ratio was 1.30 (0.7 to 2.30) in the case-control studies. The funnel plots suggested that publication bias was unlikely to be an explanation for these findings. No studies investigated the association between filaggrin gene mutations and food allergy or anaphylaxis.

Conclusions Filaggrin gene defects increase the risk of developing allergic sensitisation, atopic eczema, and allergic rhinitis. Evidence of the relation between filaggrin gene mutations and atopic eczema was strong, with people manifesting increased severity and persistence of disease. Filaggrin gene mutations also increased the risk of asthma in people with atopic eczema. Restoring skin barrier function in filaggrin deficient people in early life may help prevent the development of sensitisation and halt the development and progression of allergic disease.

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INTRODUCTION

The clinical cause of atopic disorders typically involves sensitisation to food or aeroallergens in early life, progressing to eczema and wheeze within the first two years and often leading to other manifestations of atopic allergic disease. Reports have suggested a key role of the protein filaggrin in maintaining an effective skin barrier against the environment.[1] Mutations in the profilaggrin gene resulting in loss of function occur in up to 10% of western European and North American populations.

Information about the association between filaggrin gene defects and allergic disorders is accruing rapidly. The initial focus was on atopic eczema.[2] Filaggrin gene defects should also increase the risk of developing pathophysiologically related conditions such as food allergy, allergic rhinitis, and asthma. We undertook a systematic review and meta-analysis to investigate the relation between filaggrin gene mutations, allergic sensitisation, and a range of atopic allergic disorders.

METHODS

We considered as eligible for inclusion any type of genetic epidemiological study in humans of all ages and ethnic groups that investigated the association between filaggrin gene defects and allergic sensitisation or allergic disorders (see bmj.com for search strategy). The clinical outcome measures of interest were atopic eczema or dermatitis, food allergy, asthma, allergic rhinitis, and anaphylaxis, along with immunological variables relating to the risk of allergic sensitisation as assessed by positive skin prick testing or increased levels of allergen specific IgE.

We developed a checklist for assessing the quality of the studies, considering the variables of participant selection, validity of the approach to genotyping, population stratification, and other statistical considerations.[3 4] Depending on the overall risk of drawing biased conclusions we classified studies as being of high, medium, or poor quality.

As the two common filaggrin gene mutations R501X and 2282del4 are believed to have equivalent biological

effects most of the studies analysed for a combined genotype effect along with an analysis of the two mutations. We initially focused on the effects of these two mutations separately and then combined.

We evaluated an overall estimate for the different outcomes for case-control studies and for family studies.[3 4] We used the normal approximation of the Mantel-Haenszel statistic. When there was a zero in the contingency table we added 0.5. We used random effects modelling to pool the odds ratios. Study heterogeneity was investigated using the I^2 statistic. If heterogeneity was detected, it was investigated using subgroup analyses when possible, focusing on the impact of study quality and disease severity as explanatory factors. Possible publication bias was assessed using funnel plots.

RESULTS

Overall, 24 of 319 identified papers were eligible for inclusion (see bmj.com).[w1-w24] No studies were identified that investigated the association between filaggrin gene defects and food allergies or anaphylaxis.

Sensitisation

Two case-control analyses[w12 w23] and seven familial analyses[w4 w6 w8 w12] investigated the association between filaggrin gene defects and allergic sensitisation.

Case-control studies

Pooled data from the two case-control studies[w12 w23] gave an overall odds ratio for the combined genotype of 1.57 (95% confidence interval 1.20 to 2.07; see bmj.com). Heterogeneity was significant (P=0.001) but could not be investigated owing to too few studies.

Family studies

One family study[w8] analysed two family panels and presented results for each panel and for the panels combined. One family study[w6] reported P values only and was not included in the meta-analysis.

Pooled data for the combined genotype from the other family studies gave an overall odds ratio of 1.91 (1.44 to 2.54; see bmj.com). Heterogeneity was significant (I^2=72.20; P<0.001).

The overall odds ratio for R501X was 2.47 (1.70 to 3.59) and for 2282del4 was 2.25 (1.85 to 2.75; see bmj.com). Heterogeneity was not significant (P=0.11 and P=0.83, respectively).

Atopic eczema and atopic dermatitis

Twenty case-control analyses[w1-w3 w5 w7-w10 w12-w19 w21-w23] and eight familial analyses[w4 w8 w12 w15 w21 w24] investigated the association between filaggrin gene defects and atopic dermatitis. Most of the studies were on western European populations, but three case-control studies[w7 w18 w21] and one family study[w21] were on a Japanese population and one case-control study[w2] on a North American population.

Case-control studies

One case-control study[w5] was not included in the meta-analysis because an odds ratio and 95% confidence interval could not be calculated. Four other case-control studies[w7 w8 w18 w21] were also not included. Two were on a Japanese population, and R501X and 2282del4 were absent in 253 participants.[w7 w18] One study also showed a statistical association between filaggrin gene mutations, identified in the Japanese population, and atopic dermatitis.[w21] Another study[w8] was not included in the meta-analysis because the population comprised affected and unaffected offspring from family panels in a case-control setting. The case-control studies included in the meta-analysis were all on western European or North American populations.

Using a random effects model the overall odds ratio for the combined genotype was 4.78 (3.31 to 6.92; see bmj.com). Heterogeneity was significant (P=0.001). The funnel plot showed no evidence of publication bias.

The overall odds ratio for R501X was 4.32 (2.85 to 6.56) and for 2282del4 was 4.61 (3.07 to 6.93; see bmj.com). Significant heterogeneity was observed (I^2=78%, P<0.001, and I^2=75%, P<0.001, respectively). Subgroup analysis for the combined genotype with studies excluded that were judged to be at high risk of bias gave an odds ratio of 4.71 (3.04 to 7.31; see bmj.com), with evidence of significant heterogeneity still showing between studies (I^2=86.0%; P<0.001).

Family studies

Seven familial analyses were on western European populations[w4 w8 w12 w15 w24] and one on a Japanese population.[w21] One of the studies[w8] analysed two different family panels and presented results for the panels separately and combined. The Japanese study reported P values only and was not included in the meta-analysis.[w21]

The overall odds ratio for the combined genotype using random effects modelling was 1.99 (1.72 to 2.31; see bmj.com). Heterogeneity was not significant (P=0.21). The funnel plot did not suggest publication bias. The overall odds ratio for R501X was 2.44 (1.98 to 3.02) and for 2282del4 was 2.27 (1.91 to 2.69; see bmj.com). Heterogeneity was not significant (P=0.46 and P=0.83, respectively).

Cohort study

One cohort study[w20] investigated the interaction between filaggrin loss of function mutations and environmental exposures in the development of eczema. The data were from two birth cohorts (Denmark and the United Kingdom). Filaggrin gene mutations increased the risk of eczema during the first year of life: hazard ratios 2.26 (95% confidence interval 1.27 to 4.00) and 1.95 (1.13 to 3.36), respectively.

Allergic rhinitis

People without atopic dermatitis or eczema

Three case-control studies investigated the association between filaggrin gene defects and allergic rhinitis in people without atopic dermatitis.[w12 w22 w23] One[w22] reported a P value for the combined genotype only. Data were pooled from the other two studies, in German populations.[w12 w23] Using a random effects model the overall odds ratio for the combined genotype was 1.78 (1.16 to 2.73; see bmj.com).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Atopic allergic disorders affect up to a third of people worldwide

Eczema is often the herald condition in those with allergic conditions, typically beginning in the first year of life

Filaggrin gene defects, present in up to one in 10 western Europeans and North Americans, are possible predisposing factors in the development of atopic eczema

WHAT THIS STUDY ADDS

Filaggrin gene defects increase the risk of allergic sensitisation, suggesting that defective function of the skin barrier may be fundamental in people with allergic disorders

Filaggrin gene defects are associated with a significantly increased risk of atopic eczema, allergic rhinitis, and asthma in people with eczema

Interventions to restore the barrier function of the skin or measures to avoid allergens in filaggrin defective infants need investigation

People with atopic dermatitis or eczema

Three case-control studies[w12 w16 w23] and two family studies[w12 w24] investigated the association between filaggrin gene defects and allergic rhinitis in people with atopic dermatitis.

All three case-control studies were in German populations. One study[w16] reported no original data for allergic rhinitis but only odds ratios adjusted for age and sex (4.04, 2.11 to 7.72); this study was not included in the meta-analysis. Data were pooled from the other two studies.[w12 w23] The overall estimated odds ratio for the combined genotype was 2.84 (2.08 to 3.88; see bmj.com).

One family study[w12] was carried out on a German population and another on a Swedish population.[w24] Pooled data for the combined genotype gave an overall odds ratio of 2.46 (1.61 to 3.76).

Asthma

People without atopic dermatitis or eczema

Five case-control studies[w1 w8 w12 w22 w23] and one family study[w6] investigated the association between filaggrin gene defects and asthma in people without atopic dermatitis. The five case-control studies were on western European populations, whereas the family study was on a North American population. None of these studies showed a significant association between filaggrin gene defects and asthma. One family study[w6] reported an odds ratio for the combined genotype of 1.0 (0.51 to1.96; P=1.00).

Data were pooled from the case-control studies to estimate an overall odds ratio. One study[w8] was not included in this meta-analysis because the population comprised affected and unaffected offspring from family panels in a case-control setting. Another study[w22] was also not included because it reported a P value for the combined genotype only. After pooling the data from the remaining studies,[w1 w12 w23] the overall odds ratio for the combined genotype was 1.30 (0.73 to 2.30; see bmj.com). Heterogeneity was not significant (P=0.37).

People with atopic dermatitis or eczema

Six case-control studies and seven family studies investigated the association between filaggrin gene defects and asthma in people with atopic dermatitis. All the studies except one, were on Western European populations; the remaining study was on a North American population.[w6]

Case-control studies

One case-control study[w16] was not included in the meta-analysis because the researchers reported no original data. Another study[w22] reported a P value for the combined genotype. Pooled data for the combined genotype from the other four case-control studies gave an overall odds ratio of 2.79 (1.77 to 4.41; see bmj.com). Heterogeneity was significant (P<0.001). The funnel plot did not suggest publication bias.

Family studies

Seven family studies investigated the association between filaggrin gene defects and asthma in people with atopic dermatitis. One study[w8] analysed two family panels and presented results for each panel separately as well as combined. Pooled data for the combined genotype from the family studies gave an overall odds ratio of 2.30 (1.66 to 3.18; see bmj.com). Heterogeneity was significant (P<0.001). Publication bias was unlikely.

An overall odds ratio for R501X was 2.30 (1.72 to 3.09; see bmj.com) and for 2282del4 was 2.82 (2.19 to 3.64; see bmj.com).

DISCUSSION

In this systematic review and meta-analysis we found that filaggrin gene defects increase the risk of developing sensitisation, atopic eczema or atopic dermatitis, and allergic rhinitis. The risk of those with but not without atopic eczema developing asthma was also increased. These findings provide strong evidence that, at least in a subset of those with allergic problems, the filaggrin gene defect may be the fundamental predisposing factor in the development of eczema and the initial sensitisation and progression of allergic disease.

The key strengths of this work include the comprehensive searches and assessment for a range of clinical and immunological outcome measures. This approach does, in theory at least, increase the possibility of type 1 errors, although we focused on the pooled odds ratios and 95% confidence intervals of data obtained from the meta-analyses thus allowing readers to judge the strength of the associations identified. We may have failed to identify some studies, particularly those with negative findings. Although we attempted to assess for publication bias, we recognise that funnel plots have relatively low power to detect such bias, particularly when there are relatively few studies included in these plots.[5]

Overall this work underscores the importance of filaggrin gene defects in increasing the risk of sensitisation and a range of allergic clinical phenotypes, most probably through exposure to allergens through the skin. Our findings suggest that filaggrin is a robust biomarker for allergic conditions.

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Overall and cancer related mortality among patients with ocular inflammation treated with immunosuppressive drugs: retrospective cohort study

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ABSTRACT

Context Whether immunosuppressive treatment adversely affects survival is unclear.
Objective To assess whether immunosuppressive drugs increase mortality.
Design Retrospective cohort study evaluating overall and cancer mortality in relation to immunosuppressive drug exposure among patients with ocular inflammatory diseases. Demographic, clinical, and treatment data derived from medical records, and mortality results from United States National Death Index linkage. The cohort's mortality risk was compared with US vital statistics using standardised mortality ratios. Overall and cancer mortality in relation to use or non-use of immunosuppressive drugs within the cohort was studied with survival analysis.
Setting Five tertiary ocular inflammation clinics.
Patients 7957 US residents with non-infectious ocular inflammation, 2 340 of whom received immunosuppressive drugs during follow up.
Exposures Use of antimetabolites, T cell inhibitors, alkylating agents, and tumour necrosis factor inhibitors.
Main outcome measures Overall mortality, cancer mortality.
Results Over 66 802 person years (17 316 after exposure to immunosuppressive drugs), 936 patients died (1.4/100 person years), 230 (24.6%) from cancer. For patients unexposed to immunosuppressive treatment, risks of death overall (standardised mortality ratio 1.02, 95% confidence interval [CI] 0.94 to 1.11) and from cancer (1.10, 0.93 to 1.29) were similar to those of the United States population. Patients who used azathioprine, methotrexate, mycophenolate mofetil, ciclosporin, systemic corticosteroids, or dapsone had overall and cancer mortality similar to that of patients who never took immunosuppressive drugs. In patients who used cyclophosphamide, overall mortality was not increased and cancer mortality was non-significantly increased. TNF inhibitors were associated with increased overall (adjusted HR 1.99, 95% CI 1.00 to 3.98) and cancer mortality (adjusted HR 3.83, 1.13 to 13.01).
Conclusions Most commonly used immunosuppressive drugs do not seem to increase overall or cancer mortality. Our results suggesting that tumour necrosis factor inhibitors might increase mortality are less robust than the other findings; additional evidence is needed.

INTRODUCTION

A common dilemma faced by patients with inflammatory diseases is whether the benefits of systemic immunosuppressive therapy warrant the associated risks. Of particular concern is the possibility of inducing a life threatening illness, such as cancer. Observational studies—which provide most of the available evidence on the topic—are potentially subject to indications-for-treatment bias, because the conditions serving as the indication for immunosuppression themselves are often associated with an intrinsically higher risk of mortality or cancer.[1]

Available reports about the risk of mortality after immunosuppressive therapy outside the transplant setting are limited. Observational studies in patients with rheumatoid arthritis have found no increased risk of mortality associated with ciclosporin or tumour necrosis factor (TNF) inhibitors.[2-4] Reports differ regarding whether use of corticosteroids increases[5-8] or does not increase[9 10] mortality risk.

More information is available about the risk of cancer after immunosuppressive treatment.[1] The weight of evidence suggests that use of azathioprine and methotrexate for inflammatory diseases does not substantially increase the overall risk of cancer; the limited information about mycophenolate mofetil is also encouraging. Data about T cell inhibitors are limited outside the transplant setting.[1 2 11] Strong evidence exists for an increased risk of skin, haematological, and bladder cancers (with cyclophosphamide) in connection with alkylating agents[1] and a few reports have indicated that mortality from all types of cancer is increased following treatment with such drugs.[12 13] Evidence that TNF

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inhibitor therapy increases cancer risk is mixed, but studies with longer term follow up suggest no increased overall risk. [3 14-18]

Non-infectious ocular inflammatory diseases provide a model system wherein the disease serving as the indication for immunosuppression seems unlikely to confer an increased risk of cancer or mortality. Here we report the results of a large scale retrospective cohort study evaluating the relation between immunosuppressive treatments and mortality in these patients.

METHODS

All patients with a non-infectious ocular inflammatory diagnosis seen at four academic ocular inflammation practices in the United States during the years 1979-2005 and an approximate 40% random sample of such patients at a fifth practice contributed to this analysis.

The centres directly managed immunosuppression in most instances and kept detailed records. Data about demographic, clinical, and treatment characteristics were obtained from these records. Use of immunosuppressive agents before cohort entry was noted along with the dosages of immunosuppressive agents and corticosteroids at all clinic visits. Additional details about this study's methods have been published previously.[19]

Data on mortality incidence during 1979-2005 inclusive were obtained by linkage of patient identifiers to the US National Death Index.[20] Causes of death obtained from death certificates are included with the linkage report.

Statistical analysis

We compared overall and cancer mortality in the cohort with that in the general population (US vital statistics). We calculated standardised mortality ratios (SMRs) and standardised cancer mortality ratios adjusted for age, race, and sex.

For the within cohort survival analysis, Cox regression[21] was used to adjust for potentially confounding variables: age, race, sex, smoking status, site of ocular inflammation, systemic inflammatory disease diagnoses, bilateral ocular inflammation, and other comorbidities. Cox models were developed for each immunosuppressive agent, and for each class of agents. Cox models evaluating cumulative dose and highest observed dose also were constructed.

RESULTS

During 1979-2005 inclusive, 10 885 patients were seen at the five participating centres. Of these, 2928 were not randomly sampled or were resident outside the United States, where mortality could not have been ascertained. The remaining 7957 were observed over 68 751 visits, spanning 14 910 person years at the clinical centres. Of these, 2340 were treated with immunosuppressive drugs. Follow-up for mortality using the National Death Index through 2005 covered 66 802 person years.

During follow-up, 936 deaths occurred, 230 (24.6%) of which were attributed to cancer. Of these, 323 deaths occurred among patients exposed to immunosuppressive drugs and 613 in unexposed patients. The cohort's overall mortality risk—adjusted only for age, sex, and race—was similar to that for the US population, both for patients unexposed to immunosuppressive therapy (SMR 1.02, 95% confidence interval [CI] 0.94 to 1.11) and for the cohort as a whole (1.03, 0.96 to 1.10). Similarly, overall cancer mortality was similar to that of the US population both for cohort members unexposed to immunosuppressive drugs (cancer specific SMR 1.10, 95% CI 0.93 to 1.29) and for the whole cohort (1.07, 0.94 to 1.23) (see bmj.com).

The relation of immunosuppressive therapy to overall and cancer mortality is summarised in fig 1 and fig 2. Non-treatment factors that were consistently associated with increased mortality risk in the within cohort comparisons (and were adjusted for in the models) included increasing age, African-American race, higher Charlson index score, active smoking, and a diagnosis of Wegener's granulomatosis or rheumatoid arthritis.

After adjustment for confounding, the antimetabolites were not associated with a substantial increase in overall mortality (fully adjusted hazard ratio 1.08, 95% CI 0.86 to 1.37) or cancer mortality (0.89, 0.54 to 1.48). Individual analyses for the most commonly used individual antimetabolites—azathioprine, methotrexate, and mycophenolate mofetil—also showed no association with increased risk of overall or cancer mortality.

Likewise, the fully adjusted within cohort comparison found no increased overall mortality risk associated with T cell inhibitors (fully adjusted hazard ratio 0.81, 95% CI 0.59 to 1.11). Cancer mortality was not significantly increased with T cell inhibitor therapy either (0.78, 0.38 to 1.59). Individual results for ciclosporin were similar to the overall results for T cell inhibitors.

Alkylating agents were not associated with significantly increased overall mortality in the within cohort comparisons (fully adjusted hazard ratio 1.17, 95% CI 0.85 to 1.61), but all-cancer mortality was non-significantly raised (1.74, 0.91 to 3.32). Comparison of overall and cancer mortality with that of the general US population gave similar results (SMR 1.06, 95% CI 0.88 to 1.26; cancer specific SMR 1.42, 95% CI 0.99 to 1.98). Findings for cyclophosphamide followed similar patterns to those for alkylating agents as a class. Only 87 patients had been treated with chlorambucil, limiting statistical precision for evaluation of its association with overall and cancer mortality.

TNF inhibitors were associated with significant increases both in overall mortality (fully adjusted hazard ratio 1.99, 95% CI 1.00 to 3.98) and cancer mortality (3.83, 95% CI: 1.13 to 13.01). Comparisons with mortality in the US general population yielded similar results for both overall (SMR 2.62, 95% CI 1.30 to 4.71) and cancer mortality (cancer specific SMR 4.05, 95% CI 1.28 to 9.53). Estimated risk ratios for etanercept and infliximab were similar in magnitude, but were non-significant, with a smaller number of observations. Little information was available about adalimumab, which was introduced shortly before 2005.

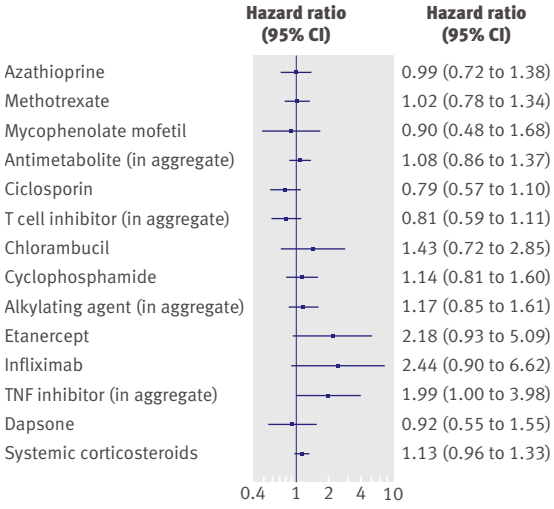

Fig 1 | Adjusted relative hazard of all cause mortality for each immunosuppressive agent and class of agents studied

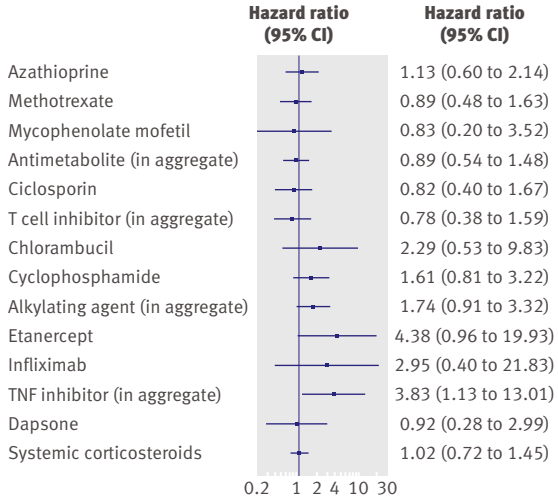

Fig 2 | Adjusted relative hazard of mortality attributed to cancer for each immunosuppressive agent and class of agents studied

Systemic corticosteroid therapy was not associated with increased overall (hazard ratio 1.13, 95% CI 0.96 to 1.33) or cancer mortality (1.02, 0.72 to 1.45) after adjusting for confounding. Patients exposed to dapsone likewise had no significant change in overall (0.92, 0.55 to 1.55) or cancer mortality (0.92, 0.28 to 2.99) in the fully adjusted within cohort analyses.

Evaluation of dose response relations for individual antimetabolites, T cell inhibitors, alkylating agents, dapsone, and systemic corticosteroids did not show increasing risks of overall or cancer mortality with increasing cumulative dose or at a dose threshold, nor with increasing highest observed dose. The data were insufficient to evaluate these relations for TNF inhibitors.

DISCUSSION

We found no significantly increased risk of death or of death from cancer among patients with ocular inflammation who had received treatment with antimetabolites, T cell inhibitors, dapsone, or systemic corticosteroids. Treatment with cyclophosphamide was not associated with significant increases in overall mortality, but there was a non-significant suggestion of increased cancer mortality. Data about treatment with TNF inhibitors were less methodologically robust than those for other drugs, but observations of significant increases in overall mortality and cancer mortality after TNF inhibitor therapy add to concerns about these treatments, especially in patients also treated with alkylating agents, and require further investigation.

Strengths and weaknesses of the study design

The eye disease indication for use or non-use of immunosuppression was a non-lethal disease, overcoming the causal pathway of indications-for-treatment bias as effectively as possible outside a randomised trial.[19]

Ascertainment of overall and cancer mortality using the National Death Index was probably excellent.[20 22-24] The duration of follow-up after exposure was favourable for all agents except mycophenolate mofetil and the TNF inhibitors; exclusion of patients with less than eight years' follow-up for mortality did not increase risk ratios, suggesting that the amount of follow-up time was sufficient to ascertain overall and cancer mortality for the other drugs.

For mycophenolate mofetil, chlorambucil, and TNF inhibitors the information available for analysis was less extensive than the other drugs. Additional follow-up or more observations would be valuable for evaluation of these drugs.

Implications of the study

Patients with ocular inflammation who take azathioprine, methotrexate, ciclosporin, dapsone, and systemic corticosteroids most likely do not increase their risk of mortality or cancer mortality substantially. Longer term follow-up of the cohort would be valuable to obtain more data about mycophenolate mofetil, a newer drug for which there was less experience, but the available data do not suggest increased overall or cancer mortality. These conclusions should be generalisable to other disease indications for immunosuppressive treatment unless a disease-treatment interaction that increases the risk of death exists for other diseases, which seems unlikely.

Our negative results are broadly consistent with published work on the risk of cancer with the antimetabolites azathioprine, methotrexate, and mycophenolate mofetil.[1] In contrast to a previous report in patients who were treated with psoralen and ultraviolet A,[11] our results, from a substantially larger cohort, suggest that ciclosporin does not increase overall or cancer mortality risk. The literature has been mixed regarding whether systemic corticosteroids increase the risk of mortality.[5-10] Our results support the view that systemic corticosteroid treatment does not itself increase the risk of overall or cancer mortality, but rather that the systemic disease that serves as the indication for such treatment increases mortality in these patients. Likewise, dapsone therapy does not seem to increase overall or cancer mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Few data are available about whether overall mortality or cancer mortality is raised after treatment with immunosuppressive agents for inflammatory diseases

Some findings suggest that overall cancer incidence may be increased with alkylating agents and with tumour necrosis factor (TNF) inhibitors, but most reports suggest that it is not substantially raised with the other agents

WHAT THIS STUDY ADDS

Use of antimetabolites, T cell inhibitors, dapsone, and systemic corticosteroids does not seem to increase overall or cancer related mortality.

Use of alkylating agents was not associated with increased overall mortality, but cancer related mortality was non-significantly increased.

Preliminary data suggest that overall and cancer mortality may be increased with TNF inhibitors; these findings should be confirmed in additional studies in view of methodological limitations of our study for this drug class

In nearly 500 patients treated with alkylating agents, cancer mortality was not increased to a statistically significant degree, but risk ratios were high and the confidence intervals only narrowly included 1.0. Our observations could be consistent with a moderate increase in overall cancer mortality[1 12 13] but cannot be taken as conclusive without expansion of the cohort. Cyclophosphamide results were similar to the overall alkylating agent results.

Our data about the recently introduced TNF inhibitors were limited in number of patients (about 200) and duration of follow-up (median 2.8 years). However, the large adverse effects we observed add to concerns that use of these agents may substantially increase overall and cancer mortality. Our result is concordant with those of the previous meta-analysis of randomised trial data,[14] but is inconsistent with those of four large observational studies,[3 15-17] each of which found no increased overall cancer risk. Our data for TNF inhibitors are less robust than for the other agents, because the majority had systemic inflammatory diseases (thus the problem of potential indications-for-treatment bias was not completely avoided for these agents). The apparent strength of the observed adverse effects indicates a need for additional evaluation of the potential risks of these widely used agents.

Contributors: see bmj.com

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Competing interests: JTR has received ≤$10 000 for consulting fees or paid advisory boards for Abbott Laboratories (ciclosporin, adalimumab) and Novartis (ciclosporin), and has a research grant from Abbott Laboratories; EBS has received a research grant from Abbott Laboratories; DAJ has received ≤$10 000 for consulting fees or paid advisory boards for Novartis. JTR and EBS have received a research grant from Centocor (infliximab); CSF reports having received fees of ≤$10,000 for speaking at the invitation of Centocor. JTR reports equity ownership/stock options >$10 000 in Amgen (etanercept). JHK, JPD, CSF, JTR, and EBS previously participated in a clinical trial of a competing product, fluocinolone acetonide implant, sponsored by Bausch & Lomb; JHK, JPD, CSF, DAJ, RBN, and JET are participating in an NIH sponsored study comparing this product with systemic therapy for uveitis, and GAL-C previously participated in this trial; Bausch & Lomb is providing a limited amount of drug product in support of this study.

Ethical approval: Institutional review board approval was granted and maintained at all participating sites throughout the study.

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Household ownership and use of insecticide treated nets among target groups after implementation of a national voucher programme in the United Republic of Tanzania: plausibility study using three annual cross sectional household surveys

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EDITORIAL
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ABSTRACT

Objectives To evaluate the impact of the Tanzania National Voucher Scheme on the coverage and equitable distribution of insecticide treated nets, used to prevent malaria, to pregnant women and their infants.

Design Plausibility study using three nationally representative cross sectional household and health facility surveys, timed to take place early, mid-way, and at the end of the roll out of the national programme.

Setting The Tanzania National Voucher Scheme was implemented in antenatal services, and phased in on a district by district basis from October 2004 covering all of mainland Tanzania in May 2006.

Participants 6115, 6260, and 6198 households (in 2005, 2006, and 2007, respectively) in a representative sample of 21 districts (out of a total of 113).

Interventions A voucher worth $2.45 (£1.47, €1.74) to be used as part payment for the purchase of a net from a local shop was given to every pregnant woman attending antenatal services.

Main outcome measures Insecticide treated net coverage was measured as household ownership of at least one net and use of a net the night before the survey. Socioeconomic distribution of nets was examined using an asset based index.

Results Steady increases in net coverage indicators were observed over the three year study period. Between 2005 and 2007, household ownership of at least one net (untreated or insecticide treated) increased from 44% (2686/6115) to 65% (4006/6198; P<0.001), and ownership of at least one insecticide treated net doubled from 18% (1062/5961) to 36% (2229/6198) in the same period (P<0.001). Among infants under 1 year of age, use of any net increased from 33% (388/1180) to 56% (707/1272; P<0.001) and use of an insecticide treated net increased from 16% (188/1180) to 34% (436/1272; P<0.001). After adjusting for potential confounders, household ownership was positively associated with time since programme launch, although this association did not reach statistical significance (P=0.09). Each extra year of programme operation was associated with a 9 percentage point increase in household insecticide treated net ownership (95% confidence interval −1.6 to 20). In 2005, only 7% (78/1115) of nets in households with a child under 1 year of age had been purchased with a voucher; this value increased to 50% (608/1211) in 2007 (P<0.001). In 2007, infants under 1 year in the least poor quintile were more than three times more likely to have used an insecticide treated net than infants in the poorest quintile (54% *v* 16%; P<0.001).

Conclusions The Tanzania National Voucher Scheme was associated with impressive increases in the coverage of insecticide treated nets over a two year period. Gaps in coverage remain, however, especially in the poorest groups. A voucher system that facilitates routine delivery of insecticide treated nets is a feasible option to "keep up" coverage.

INTRODUCTION

Strategies for delivering insecticide treated nets to prevent malaria have been controversial, with debates over whether nets should be provided through routine health services or through stand alone campaigns, whether they should be distributed through public or private channels, and whether they should be free, partially subsidised, or sold at commercial prices.[1-4] Concerns have been expressed about whether campaign based distribution strategies (so called "catch up" schemes) that aim to accelerate coverage) will ensure "temporal equity"—that is, maintain coverage between campaigns—and sustain coverage over time.[5 6] On the other hand, routine distribution strategies that use either the health system or commercial distribution networks might be better placed than campaign strategies to sustain ("keep up") coverage over time.

In Tanzania, a national strategy provides subsidised nets targeted at vulnerable groups alongside support to the commercial distribution system.[7] From 2002 until 2007, a social marketing project contributed to the development of the commercial market and worked with Tanzanian net manufacturers to distribute their products and provide subsidised insecticide for bundling with untreated nets.

This national strategy includes the Tanzania National Voucher Scheme, which is a targeted programme that aims to create a stable and predictable demand for insecticide treated nets in even the most remote locations. Under the scheme, every pregnant woman who attends antenatal care is eligible to receive a voucher that can be used as part payment for an insecticide treated net (a conventional net bundled with a package of insecticide) from any authorised shop.

Health facilities also distribute free insecticide retreatment kits to infants when they attend for measles

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vaccination. In addition to national level activities, smaller local schemes have also distributed free nets. Most notably, a free net distribution scheme targeting children under 5 years of age linked to a measles campaign in took place in 2005.[8]

The objectives of this study are to assess the changes in the level and socioeconomic distribution of insecticide treated net coverage over the period 2005-2007, during which the voucher scheme was initiated and taken to national scale, and to examine the link between programme duration and change in household net ownership as a measure of programme impact.

METHODS

The study uses a plausibility design based on three nationally representative cross sectional household and health facility surveys, timed to take place early, mid-way, and at the end of the roll out of the national voucher programme.[9 10] We compared absolute levels and changes in net coverage in areas with and without the programme over three successive years (2005, 2006, and 2007). The programme was rolled out gradually between October 2004 and May 2006, starting in districts near to Dar es Salaam and ending with the remote districts in the west. This phased roll out was necessary because of the size of the country and allowed us to compare areas with and without the voucher scheme at three points in time.

Firstly, we examined aggregate changes in net coverage over time. Secondly, we assessed within district changes in net ownership, rather than changes in absolute levels. These within district changes were compared with the length of time that the programme had been operating in each district. Thirdly, we used reported source of net to attribute nets to the voucher system and to assess the degree of penetration of voucher nets over time.

This paper reports the findings from the household and facility surveys. These surveys were designed to produce nationally representative estimates of key indicators of net coverage. Sample size was set to estimate the use of insecticide treated nets among children under 5 years and infants aged 0-11 months (under 1 year) in each district with reasonable precision (plus or minus 10% for under fives and plus or minus 20% for under ones) and at national level with correspondingly greater precision (plus or minus 2% for under fives and plus or minus 5% for under ones), assuming a coverage level of 50% and a design effect of two. The surveys were conducted in 21 randomly selected districts, stratified by planned date of launch of the scheme. See bmj.com for sampling strategy in the districts.

The surveys took place at the same time each year (July-August), after the rainy season. An interviewer administered questionnaire was used to collect information from the household head, all women aged 15-49, and carers of all children aged under 5 years. A facility survey was conducted at the reproductive and child health centre serving each cluster to collect information about service availability and use.

An index of socioeconomic status was constructed on data about housing conditions and household ownership of a selection of assets,[11] and households divided into quintiles. Clusters were classified as rural, semi-urban, or urban.

The coverage analysis distinguishes between "any net" and "insecticide treated net". We focus on changes in household ownership of nets and use of nets by pregnant women and infants aged 0-11 months (that is, under 1 year of age), to trace the impact of the voucher system.

Multivariate regression was used to explore the impact of the voucher scheme on household ownership of insecticide treated nets. The length of time the programme was implemented in each district was regressed on the change in household ownership of insecticide treated nets at district level between 2005 and 2007. We included covariates to control for three potential confounders: (1) the level of net ownership in the district in 2005, which was a proxy for socioeconomic status and allowed a test of whether districts with high starting levels of coverage would see lower programme achievements; (2) whether a district was classified as "epidemic prone," which we would expect to be associated with low mosquito nuisance and, therefore, a lower demand for nets; and (3) whether the district had been the beneficiary of a free net campaign in 2005.

RESULTS

National level changes in net coverage

Around 6200 households were successfully interviewed in each of the three surveys. Refusals were low: 86/6285 (1.4%), 33/6293 (0.5%), and 67/6265 (1.1%) in 2005, 2006, and 2007, respectively.

Steady increases were observed in national coverage of any net and insecticide treated nets, measured both as household ownership of at least one net and use of a net the night before the survey. Household ownership of any net increased significantly from 44% (2686/6115) in 2005 to 65% (4006/6198) in 2007 ($P<0.001$), and treated net ownership increased from 18% (1062/5951) to 36% (2229/6198; $P<0.001$). Over the same period, use of any net among infants under 1 year of age increased from 33% (388/1180) to 56% (707/1272; $P<0.001$), and treated net use increased from 16% (188/1180) to 34% (436/1272; $P<0.001$). In all three years, use of an insecticide treated net was higher among infants under 1 year than among currently pregnant women or children under 5. For all indicators, coverage of treated nets was much lower than coverage of any net.

District by district changes in net coverage

Treated net ownership at district level varied widely at the beginning of the programme, ranging from 3% to over 50%. The largest increases in ownership of insecticide treated nets over the period 2005 to 2006 were seen in districts that received free nets in the 2005 vaccination campaign, although ownership of treated nets actually fell in two of these districts between 2006 and 2007. Seven other districts that did not benefit from large scale distribution of free nets saw large increases (in excess of 20 percentage points) in ownership of insecticide treated nets between 2005

WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of insecticide treated nets is low in many settings, despite their proved effectiveness and cost effectiveness at preventing malaria

Some success has been achieved through "campaign" style distribution systems, but few systems have proved able to deliver nets via routine contact with health services on a national scale

Vouchers are seen as a possible mechanism for delivering public health services, but the few existing programmes have operated on a small scale

WHAT THIS STUDY ADDS

Use of insecticide treated nets has increased substantially in all groups targeted by the Tanzanian National Voucher Scheme—one of the first to operate at a national scale in a low income setting—although coverage remains inequitable

A voucher scheme is a feasible option for delivery of nets through routine systems

and 2007. In 2005, the five districts classified as being "epidemic prone" had a mean level of net ownership of 10%, compared with 20% in districts that were not classed as epidemic prone (P=0.12). In addition, the mean increase in ownership of insecticide treated nets in the epidemic prone districts was only 11 percentage points compared with 20 percentage points in districts that were not classed as epidemic prone (P=0.04).

The regression analysis indicated that districts with a lower starting level of household ownership in 2005 experienced marginally smaller increases in household ownership over the period 2005 to 2007 (0.35 percentage points, 95% CI −0.73 to 0.03; P=0.07). The change in ownership in epidemic prone districts was 11.2 percentage points smaller than in districts that were not classed as epidemic prone (95% CI −20.3 to −2.2; P=0.02). Longer exposure to the scheme was associated with larger increases in ownership (P=0.09), although this finding is only statistically significant at the 10% level. Each extra year of exposure to the programme was associated with an additional 9 percentage point increase in insecticide treated net ownership (95% CI −1.6 to 20).

Penetration of voucher nets

There was strong evidence of increased ownership of nets purchased with vouchers in households with target group members compared with households that had no target group members (table).

Inequality in use of insecticide treated nets

Although use of treated nets seems to have increased in all socioeconomic quintiles, large differences remain between the poorest (Q1) and least poor (Q5) quintiles. The equity ratio for treated net use improved from 0.11 in 2005 to 0.29 in 2007; however, infants in the least poor quintile were still more than three times more likely to use a treated net as those in the poorest group.

DISCUSSION

The Tanzania National Voucher Scheme has successfully delivered subsidised insecticide treated nets to vulnerable groups through routine health services and considerably increased the number of mothers and infants using an insecticide treated net, demonstrating that a voucher system is a feasible option for contributing to "keep up" of net coverage.

A number of findings support the conclusion that at least part of the gradual increase in net coverage can be attributed to the voucher scheme. Firstly, the largest improvement in net use was among infants under 1 year of age, who would be expected to benefit most from a voucher scheme targeted at pregnant women. Secondly, districts with longer exposure to the programme tended to have larger increases in household ownership of nets, with a 9 percentage point increase for every year of programme operation. Thirdly, the share of voucher nets in households with target group members increased steadily over the period 2005 to 2007. In addition, there is evidence that the intervention was implemented fairly well in health facilities throughout the country and reached the majority of pregnant women (data not shown).

Finally, we have found no evidence to support alternative explanations for this increase in coverage: there was no dramatic improvement in incomes during the study period; the social marketing project operated in all districts and, therefore, could not explain the within district differences in coverage improvement; and although nets were delivered through other systems at various points during the study period, the voucher scheme was the only subsidy system operating nationwide and functioning throughout the entire study timeframe.

Strengths and limitations of the study

Strengths are that we used two different approaches to analyse the changes in coverage over time: national level changes in coverage between 2005 and 2007 among different target groups; and district by district changes in coverage (with regression analysis to relate these changes to programme duration and potential confounders at district level).

Limitations are that the national voucher scheme is not the only system delivering nets in Tanzania and it is not possible to isolate the contributions of each programme. In addition, for some districts there is no true baseline measure of coverage: the first round of

Nets reported to be purchased with a voucher in households with and without target group members

	2005		2006		2007		Design corrected P value for difference across years
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
Households with an infant under 1 year	78/1115	7 (5 to 9)	460/1209	38 (34 to 42)	608/1211	50 (46 to 54)	<0.001
Households with a child under 5 years	119/3410	3.5 (3 to 5)	691/3683	18.8 (17 to 21)	1271/3795	33.5 (31 to 36)	<0.001
Households with a currently pregnant woman	47/752	6.3 (4 to 9)	109/577	18.9 (16 to 23)	163/691	23.6 (20 to 28)	<0.001
Households with neither a child under 5 years nor a currently pregnant woman	18/2520	0.7 (0.5 to 1)	103/2415	4.3 (4 to 5)	77/2220	3.5 (3 to 4)	<0.001

evaluation surveys took place in July-August 2005, but the project began activities in October 2004. The effect of the late baseline is to underestimate the impact of the voucher scheme, however.

Conclusions and policy implications

The consistent gap between use of any net and use of a treated net suggests an urgent need to improve insecticide treatment of nets. A "catch up" campaign is required to raise coverage levels in all socioeconomic groups and is planned for 2009. The planned catch up campaign should also help to address another of the major problem of strong socioeconomic and geographic differences in coverage and use.

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Recurrence up to 3.5 years after antibiotic treatment of acute otitis media in very young Dutch children: survey of trial participants

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ABSTRACT

Objective To determine the long term effects of antibiotic treatment for acute otitis media in young children.
Design Prospective three year follow-up study within the framework of a primary care based, double blind, randomised, placebo controlled trial.
Setting 53 general practices in the Netherlands.
Participants 168 children aged 6 months to 2 years with acute otitis media.
Interventions Amoxicillin 40 mg/kg/day in three doses compared with placebo.
Main outcome measures Recurrence of acute otitis media; referral to secondary care; ear, nose, and throat surgery.
Results Acute otitis media recurred in 63% (47/75) of children in the amoxicillin group and in 43% (37/86) of the placebo group (risk difference 20%, 95% confidence interval 5% to 35%); 30% (24/78 amoxicillin; 27/89 placebo) of children in both groups were referred to secondary care, and 21% (16/78) of the amoxicillin group compared with 30% (27/90) of the placebo group had ear, nose, and throat surgery (risk difference −9%, −23% to 4%).
Conclusion Recurrent acute otitis media occurred more often in the children originally treated with amoxicillin. This is another argument for judicious use of antibiotics in children with acute otitis media.
Trial registration Netherlands Trial Register NTR1426.

INTRODUCTION

Guidelines recommend prescription of antibiotics in children with severe acute otitis media and in those under 2 years of age with bilateral acute otitis media or acute otorrhoea. For most other children with acute otitis media, initial observation is recommended.[1-3]

Initial prescription of antibiotics may shorten the course of acute otitis media,[4 5] but it may also encourage doctors' attendance in future episodes, increase pressure on doctors to prescribe, increase future use of antibiotics, and therefore increase antibiotic resistance.[6 7]

Clinical outcomes between six months and three years after randomised controlled trial. Values are numbers (percentages) unless stated otherwise

Outcome	Amoxicillin (n=78)	Placebo (n=90)	Risk difference (95% CI)	Relative risk (95% CI)
Recurrent acute otitis media	47/75 (63)	37/86 (43)	20% (5% to 35%)	1.5 (1.1 to 2.0)
Referral rate	24 (31)	27/89 (30)	0% (−14% to 14%)	1.0 (0.6 to 1.6)
Surgery rate	16 (21)	27 (30)	−9% (−23% to 4%)	0.7 (0.4 to 1.2)

Antibiotic treatment may cause an unfavourable shift towards colonisation with resistant pathogens, which are likely to promote recurrence of the infection.[8-11] We aimed to study the long term effects of antibiotics on recurrence of acute otitis media; referrals to secondary care; and ear, nose, and throat surgery.

METHODS

A primary care based, randomised, placebo controlled, double blind trial on the effects of amoxicillin compared with placebo in children with acute otitis media aged between 6 and 24 months took place in the Netherlands between February 1996 and May 1998. It included 240 children, who were followed actively for six months.[4 12]

In 2000—approximately three and half years after the start of the trial—we sent a questionnaire to parents of the participating children, asking them about episodes of recurrent acute otitis media; referral to secondary care; and ear, nose, and throat surgery. We defined the primary outcome measure as at least one episode of acute otitis media that occurred between the last study appointment at six months and the current survey. In addition, we compared the proportion of children referred to secondary care and the rate of ear, nose, and throat surgery.

We firstly looked only at risk difference and did not adjust for potential confounders. To be sure that confounding was not a problem in the post-randomisation period, we also studied the following potential confounders by using logistic regression analysis: mean age at inclusion, sex, breast feeding, number of siblings, season of inclusion, attendance at day care centre, family history of recurrent upper respiratory tract infections, (duration of) symptoms at presentation, subsequent use of antibiotics within six months, and the clinical outcome at days four and 11 and six months. We did a sensitivity analysis on the primary outcome restricted to the children in each group who did not receive antibiotics within the first six months of the post-trial follow-up period.

RESULTS

Of the 240 participants originally randomised, 168 (70%) returned the questionnaire. At this stage, about 95% of these parents were still blinded to the original treatment. The baseline characteristics of these 168 children were similar to those initially randomised.

Three years after randomisation, acute otitis media had recurred in 47/75 (63%) children in the amoxicillin group compared with 37/86 (43%) in the placebo group (risk difference 20%, 95% confidence interval 5% to 35%) (table). Logistic regression analysis showed that sex, allergy, and history of recurrent acute otitis media might be relevant confounding factors. Adjustment for these factors resulted in an adjusted odds ratio of 2.5 (95% confidence interval 1.2 to 5.0).

A similar number of children in both groups were referred to secondary care (risk difference 0%, −14% to 14%) (table). Finally, 16/78 (21%) children in the amoxicillin group compared with 27/90 (30%) in the placebo group had ear, nose, and throat surgery (risk difference −9%, −23% to 4%).

Sensitivity analysis for the primary outcome measure, comparing only those children in each group who did not receive antibiotics in the first six months of the post-trial follow-up period, showed a risk difference of 32% (13% to 51%) and an adjusted odds ratio of 4.4 (1.7 to 11.5).

DISCUSSION

We found a 20% higher rate of recurrence of acute otitis media in the amoxicillin group compared with the placebo group in the post-trial period between six months and three years after randomisation. The corresponding confidence intervals, however, are wide, so this rate must be interpreted with some caution.

Other groups have studied the effects of antibiotics up to one year and found no differences between the groups.[7 13] This seems to be in agreement with our results for the first six months of follow-up, in which we found similar recurrence rates in the amoxicillin and placebo group (51% *v* 50%; risk difference 1%, 95% confidence interval −12% to 15%).

Our findings might be explained by unfavourable changes in the colonisation of the nasopharynx as a result of the use of antibiotics,[8-11] or the use of antibiotics early in an episode of acute otitis media may impair the natural immune response and weaken the protection against further episodes.[14-16] Both possible explanations would primarily have resulted in a difference in recurrence of acute otitis media in the first six months of follow-up, which was not the case.

The major strength of our study is the fact that most parents were still blinded to the original treatment when they filled in the questionnaire. Furthermore, by using a questionnaire we measured true recurrences rather than reattendances.

Some possible limitations deserve further discussion. Under-reporting or over-reporting of acute otitis media cannot fully be precluded, so the recurrence rates might be biased; however, we would expect a similar effect in both groups. Only 70% of the parents who participated in the randomised controlled trial returned the questionnaire, which might have led to selection of otitis prone children. The baseline characteristics of the children whose parents responded were, however, similar to those of the original trial population. We did not do a Cox regression analysis, as we measured only the number of recurrent episodes after three years. As the mean follow-up times were similar in both groups, however, we do not expect that Cox regression would have changed our results. Our results can be generalised only to otherwise healthy children in well resourced settings. Acute otitis media can become a serious illness in children at risk and in those in less resourced settings, and this may call for

a more active approach to treatment. Finally, owing to the delay in reporting the results of this survey, changes in practice may have reduced the applicability of our results. As antibiotics are still widely prescribed in young children with acute otitis media,[17] however, we believe that the results of our study are still applicable.

In conclusion, recurrent acute otitis media occurred more often in the children originally treated with amoxicillin. This is another argument for judicious use of antibiotics in children with acute otitis media.

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Contributors: See bmj.com.

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Competing interest: MMR has participated in a CME accredited symposium on the burden of otitis media, which was supported by an unrestricted grant from GlaxoSmithKline.

Ethical approval: The ethics committee of the University Medical Center Utrecht approved the protocol.

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What would you ask Margaret Chan?

The spread of A/H1N1 flu has propelled Margaret Chan, director general of the World Health Organization, into the limelight. On 11 June she was on television and radio programmes across the world, declaring that "the world is now at the start of the 2009 influenza pandemic" and that "further spread is considered inevitable" (*BMJ* 2009;338:b2425, doi:10.1136/bmj.b2425).

But what do we know about the 62 year old doctor who took over the reins of the behemoth on the death of Dr Lee Jong-wook in 2006?

A profile of her in the *Financial Times* in May (www.ft.com/cms/s/0/a4fc8e58-3c01-11de-acbc-00144feabdc0.html) criticised her for not having a grand vision of reform and described her as a bureaucrat rather than a politician. But it also quoted Julio Frenk, dean of Harvard School of Public Health, as saying: "For the kind of focused response [needed during an epidemic] she's the best person we could possibly hope for."

We would like to know what you, our readers, think about Dr Chan's handling of the crisis and her performance at the head of WHO. Does Dr Chan have a vision for the future? What should her priorities be for the next three to five years? Was she wrong to insist that swine flu be renamed A/H1N1 after pressure from the farming lobby? Do her Chinese roots prevent her from dealing firmly enough with the secrecy and violations of human rights of the Chinese government?

And, above all, has WHO overreacted to the threat from flu? Simon Jenkins wrote in the *Guardian* on 29 April: "The World Health Organization, always eager to push itself into the spotlight, loves to talk of the world being 'ready' for a flu pandemic, apparently on the grounds that none has occurred for some time . . . An obligation on public officials not to scare people or lead them to needless expense is overridden by the yearning for a higher budget or more profit" (www.guardian.co.uk/commentisfree/2009/apr/29/swine-flu-mexico-uk-media1).


WHO

Put your questions to Dr Chan

Now is your chance to put your questions to Dr Chan. The *BMJ*'s Hong Kong correspondent, Jane Parry, will conduct an interview with the WHO chief in July. She would welcome your questions.

Email your questions to aferriman@bmj.com.

Annabel Ferriman

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Association between mid-life marital status and cognitive function in later life: population based cohort study

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STUDY QUESTION Is there a relation between marital status in mid-life and cognitive function in later life?

SUMMARY ANSWER People living in a couple relationship at mid-life had a reduced risk of cognitive impairment later in life.

Participants and setting

This study is part of the cardiovascular risk factors, aging and dementia (CAIDE) project, a prospective cohort study in eastern Finland.

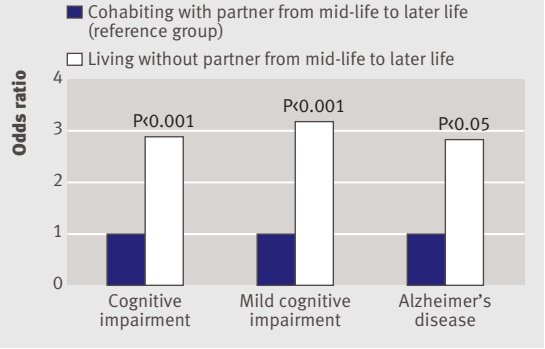
Design, size, and duration

From a random sample of 2000 survivors from earlier cohorts investigated in 1972-87 (mid-life visit), 1449 participated in the re-examination in 1998, on average 21 years later (later life visit). Data on several vascular and lifestyle related factors were collected at both times. We recorded marital status (cohabitant, single, divorced, or widowed) at mid-life and follow-up and measures of cognitive impairment (mild cognitive impairment, Alzheimer's disease, and other forms of dementia) at follow-up. Cognitive impairment was found in 139 people, of whom 82 had mild cognitive impairment and 48 had Alzheimer's disease. We also determined who carried the apolipoprotein E e4 allele. We used logistic regression to analyse the association between marital status and cognitive status later in life, progressively entering several adjustment variables.

Main results and the role of chance

People cohabiting with a partner in mid-life (mean age 50.4) had about half the risk (odds ratio 0.48, P=0.002) of any cognitive impairment later in life compared with non-cohabitants (single, separated, or widowed). These associations were even more pronounced when we combined marital status both in mid-life and later in life. Compared with cohabitants at both times, non-cohabitants both at mid-life and later in life had about three times the risk for mild cognitive impairment and Alzheimer's disease. The highest risk (odds ratio 7.67) was associated with being widowed before mid-life and still being widowed in later life compared with those who were living with a partner at both times (P=0.01). People who carried the apolipoprotein E e4 allele were especially vulnerable to Alzheimer's disease if they continued to live alone after divorcing or being widowed.

ASSOCIATION BETWEEN MARITAL STATUS FROM MID-LIFE TO LATER LIFE AND COGNITIVE IMPAIRMENT



Bias, confounding, and other reasons for caution

We adjusted for the most well known risk factors for cognitive impairment (age, education, and apolipoprotein E e4) and for risk factors measured in mid-life (including blood pressure, cholesterol concentration, body mass index, and smoking). This did not change the observed associations. Some other unknown factor of importance for dementia, such as a personality factor, might also be associated with marital status. As the main difference between groups existed between those who lived with a partner and those who were widowed, this seems unlikely. People in both of these groups decided to marry once and the widowed group did not become widowed as result of their own decision—that is, it was not self selected. Follow-up time was long, making reverse causation unlikely.

Generalisability to other populations

Differences in culture, living conditions, and genetic characteristics typically vary across populations. The general relevance of lifestyle factors for cognitive health, however, has been indicated by several other cohort studies. We therefore do not believe that these associations are limited to the investigated population.

Study funding/potential competing interests

This study was funded by EVO-grant of Kuopio University Hospital (5772720), Academy of Finland (grants 103334 and 206951), EU grant QLK-2002-172, the Swedish Council for Working Life and Social Research, the Finnish Cultural Foundation, the Foundation of Juho Vainio, the Gamla Tjänarinnor Foundation, the Helsingin Sanomain 100-vuotissäätiö, and the Gun and Bertil Stohne Foundation. The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

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