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RESEARCH

Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study

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Cite this as: *BMJ* 2008;337:a258
doi:10.1136/bmj.a258

ABSTRACT

Objective To investigate associations of dietary iron (total, haem, and non-haem), supplemental iron, and red meat with blood pressure.

Design Cross sectional epidemiological study.

Setting 17 population samples from Japan, China, the United Kingdom, and the United States participating in the international collaborative on macro-/micronutrients and blood pressure (INTERMAP).

Participants 4680 adults aged 40-59.

Main outcome measure Average of eight blood pressure readings.

Results In multiple linear regression analyses dietary total iron and non-haem iron were consistently inversely associated with blood pressure. With adjustment for potential non-dietary and dietary confounders, dietary total iron intake higher by 4.20 mg/4.2 MJ (2 SD) was associated with 1.39 mm Hg ($P<0.01$) lower systolic blood pressure. Dietary non-haem iron intake higher by 4.13 mg/4.2 MJ (2 SD) was associated with 1.45 mm Hg ($P<0.001$) lower systolic blood pressure. Differences were smaller for diastolic blood pressure. In most models haem iron intake from food was positively, non-significantly associated with blood pressure. Iron intake from combined diet and supplements yielded smaller associations than dietary iron alone. Red meat intake was directly associated with blood pressure; 102.6 g/24 h (2 SD) higher intake was associated with 1.25 mm Hg higher systolic blood pressure. Associations between red meat and blood pressure persisted after adjustment for multiple confounders.

Conclusion Non-haem iron has a possible role in the prevention and control of adverse blood pressure levels. An unfavourable effect of red meat on blood pressure was observed. These results need confirmation including in prospective studies, clinical trials, and from experimental evidence on possible mechanisms.

INTRODUCTION

The relation between iron intake and blood pressure is largely unknown. Iron might contribute to the production of reactive oxygen species, oxidative stress, and inflammation—all possibly adversely related to blood pressure levels.[1 2] We investigated associations of dietary iron intake, red meat intake, and food plus supplemental iron with blood pressure in the international collaborative study on macro-/micronutrients and blood pressure (INTERMAP).

METHODS

The study population (1996-9) comprises 4680 adults from 17 samples: Japan (n=4), China (n=3), the United Kingdom (n=2), and the United States (n=8).[3] Data were collected cross sectionally. Participants attended the research clinic on four occasions: two visits on consecutive days, a gap of three weeks, then two further consecutive visits.

Blood pressure was measured twice at each visit. At two visits height and weight were measured and questionnaire data were obtained on daily alcohol intake over the past week and other possible confounders.

At each visit, data on diet were collected using the 24 hour recall method (see bmj.com). We carried out two timed 24 hour urine collections, coinciding with the two pairs of consecutive visits.

Statistical analysis

To provide comparable data on 83 nutrients across the four countries, we converted data on food and dietary supplements into nutrient intakes by using standardised country specific food tables.[4] We calculated nutrient intakes from foods and from foods plus dietary supplements. For nutrients supplying energy we calculated intake as percentage millijoules and for others as intake per 4.2 MJ. We also calculated nutrients as amount per 24 hours. To estimate intake of haem and non-haem iron from dietary total iron intake we used an established formula,[5] taking into account the source of iron (meat, poultry, fish *v* other). We used the food data to characterise the main food groups supplying iron and to estimate each participant's intake of red meat and beef. Measurements for each participant were averaged for blood pressure and nutrient variables across the four visits, and for urinary excretions across the two 24 hour collections.

We used partial correlation to explore the associations among dietary variables, adjusted for sample, age, and sex, and pooled across countries, weighted by sample size. To examine the relations of iron intake (total, haem,

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008;337:a258.

non-haem, total plus supplements) and intake of red meat or beef (g/24 h, adjusted for energy intake) to systolic and diastolic blood pressure we used multiple linear regression analyses. Adjustment for possible confounders was done sequentially: for sample, age, sex, weight, height, reported special diet, dietary supplements, moderate or heavy physical activity (hours daily), doctor diagnosed cardiovascular disease and diabetes, and family history of hypertension (model 1 on bmj.com); plus 24 hour urinary excretion of sodium and potassium (or urinary sodium and potassium to creatinine ratios) and alcohol intake over 14 days (model 2 on bmj.com); plus levels of dietary cholesterol, saturated fatty acids, and polyunsaturated fatty acids (model 3 on bmj.com); plus intake of either animal protein, vegetable protein, dietary fibre, magnesium, phosphorus, calcium, haem iron (red meat analysis only) or non-haem iron (red meat analysis only) entered separately to avoid colinearity (models 4a-h on bmj.com). We also tested heterogeneity across countries and we assessed interactions for age and sex.

In sensitivity analyses we analysed iron from food plus dietary supplements (with and without 59 participants with a supplemental iron intake >30 mg/day); adjustment for total carbohydrate, starch, or total sugars (% MJ); use of nutrient densities of iron adjusted for energy; use of amount per 24 hours of iron intakes adjusted for energy; and exclusion of people with noticeable variability in nutrient intake or blood pressure. We transformed regression coefficients to represent difference in blood pressure for each two standard deviation higher intakes of iron, red meat, or beef. We adjusted each standard deviation for country, estimated from country adjusted analysis of variance.

RESULTS

Mean systolic blood pressure ranged from 117.2 mm Hg (Japan) to 121.3 mm Hg (China) and mean diastolic blood pressure from 73.2 mm Hg (China) to 77.3 mm Hg (UK). Mean iron consumption was higher in the United States and China (7.8 mg/4.2 MJ for both) than in the UK and Japan (6.2 mg/4.2 MJ and 5.3 mg/4.2 MJ). Mean body mass index and energy intake were lower in Japan and China, and highest in the United States.

About 6% of iron intake in the UK and United States was the haem component. In Japan and China 9% and 3% of iron intake was haem iron, with the main food source being fish (Japan 61%, China 88%). In the UK and United States meat supplied 90% and 87% of haem iron (see bmj.com). Vegetables and beans were the main food sources of non-haem iron in Japan and China and bread and cereals in the UK and United States.

Total iron intake from food was inversely related to systolic blood pressure (see bmj.com). Inverse differences were smaller for diastolic blood pressure than for systolic blood pressure. In model 3 (adjusted for multiple possible confounders) 2 SD higher total dietary iron intake (4.2 mg/4.2 MJ) was associated with 1.39 mm Hg lower systolic blood pressure and with 0.68 mm Hg lower diastolic blood pressure. The size and strength of the associations between intake of non-haem iron and blood pressure were generally stronger than those for total iron (see bmj.com).

Participants in China reported the lowest mean consumption of red meat (24 g/24 h) and had the highest prevalence (26%) of no red meat consumption on at least one of four days. Mean red meat intake over 24 hours was 39 g in Japan, 91 g in the UK, and 76 g in the United States. Consumption of red meat was positively associated with systolic and diastolic blood pressures (see bmj.com). No significant heterogeneity was observed across countries. In model 3 red meat intake higher by 2 SD (103 g/24 h) was associated with 1.25 mm Hg higher systolic blood pressure ($P<0.01$) and 0.73 mm Hg higher diastolic blood pressure ($P=0.01$). Only 5% of red meat intake was beef among participants from China compared with 33% in Japan, 40% in the UK, and 66% in the United States. When beef was analysed separately, associations with blood pressure were positive but mostly smaller (see bmj.com).

Sensitivity analyses

Only two participants from China consumed dietary supplements containing iron. Iron supplements were consumed by 5% of participants from Japan, 11% from the UK, and 31% from the United States. In Japan and the UK addition of supplementary iron resulted in small increases in total iron intake. Total iron intake from diet and supplements combined was consistently inversely associated with systolic blood pressure and diastolic blood pressure; associations were weaker than those for dietary iron alone. Red meat showed slightly stronger associations with blood pressure.

DISCUSSION

Intake of total iron and non-haem iron are inversely related to blood pressure. Direct associations of haem iron with blood pressure were not statistically significant. Red meat consumption was positively associated with blood pressure.

The relation of a high iron diet to blood pressure is largely unknown. Iron is hypothesised to play a detrimental part in atherosclerotic disease through oxidative stress and inflammation. We found an inverse relation between total dietary iron intake and blood pressure. When we separated total dietary iron into haem and non-haem components, we observed a differential effect on blood pressure; non-haem iron was inversely associated with blood pressure, whereas haem iron was mainly positively although not significantly associated with blood pressure.

Separating iron sources into the haem and non-haem components makes sense as their mechanisms of absorption differ. About 25% of haem iron compared with 2.5% of non-haem iron is absorbed in healthy people.[6]

The inverse relation of non-haem iron to blood pressure, although consistent in our multivariable analyses, may reflect correlations of non-haem iron with several other nutrients from vegetable foods. Inferences about causality are therefore premature. Although the observed differences in blood pressure

WHAT IS ALREADY KNOWN ON THIS TOPIC

Sodium intake, alcohol, and caloric imbalance have shown direct associations with blood pressure and potassium intake inverse associations

Relations between iron and blood pressure are largely unknown

WHAT THIS STUDY ADDS

Intake of total iron and non-haem iron was inversely related to blood pressure

Red meat consumption, the major food source of haem iron, was associated with higher blood pressure

associated with higher non-haem iron intake were relatively small, they have public health relevance for the general population.

Haem iron, a major component of total iron intake in Western diets, showed direct weak associations with blood pressure. Its association with blood pressure probably reflects the adverse relation of meat intake to blood pressure observed in the present and previous studies.[7-9] In our study this relation persisted after control for multiple confounders; previous studies gave no such data on potential confounders.

Limitations

Limitations of this study include dietary assessments from self reports, variation among food tables from different countries, and variability in daily dietary intake. To minimise potential errors we used standardised food tables across countries and repeated 24 hour dietary recalls and urine collections. Although some misclassification of nutrient intakes, based on four 24 hour recalls, is present, non-differential misclassification would most likely reduce observed associations between iron and blood pressure.[10 11] All data are cross sectional, thus long term influences of dietary factors on blood pressure may be underestimated. Causality cannot be inferred. Despite adjustment for confounders, we cannot exclude the possibility of residual confounding.

Conclusions

We found an inverse association of dietary total iron intake and non-haem iron intake with blood pressure. A weak direct association between haem iron and blood pressure was observed, probably reflecting the adverse relation of red meat consumption to blood pressure. Higher red meat intake was independently associated with higher blood pressure.

We thank study staff at local, national, and international centres for their efforts; a partial listing of these colleagues is given in reference 3.

Contributors: See bmj.com.

Funding: This research has been supported by grant 2-RO1-HL50490 from the US National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; by the Chicago Health Research Foundation; and by national agencies in China, Japan (Ministry of Education, Science, Sports, and Culture, grant in aid for scientific research, No 090357003), and the United Kingdom. The sponsors had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Competing interests: None declared.

Ethical approval: This study was approved by the institutional review board for each participating centre.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 7 May 2008

A model based on age, sex, and morbidity to explain variation in UK general practice prescribing: cohort study

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Cite this as: *BMJ* 2008;337:a238
doi:10.1136/bmj.a238

ABSTRACT

Objective To examine whether patient level morbidity based measure of clinical case mix explains variations in prescribing in general practice.

Design Retrospective study of a cohort of patients followed for one year.

Setting UK General Practice Research Database.

Participants 129 general practices, with a total list size of 1 032 072.

Main outcome measures Each patient was assigned a morbidity group on the bases of diagnoses, age, and sex using the Johns Hopkins adjusted clinical group case mix system. Multilevel regression models were used to explain variability in prescribing, with age, sex, and morbidity as predictors.

Results The median number of prescriptions issued annually to a patient is 2 (90% range 0 to 18). The number of prescriptions issued to a patient increases with age and morbidity. Age and sex explained only 10% of the total variation in prescribing compared with 80% after including morbidity. When variation in prescribing was split between practices and within practices, most of the variation was at the practice level. Morbidity explained both variations well.

Conclusions Inclusion of a diagnosis based patient morbidity measure in prescribing models can explain a large amount of variability, both between practices and within practices. The use of patient based case mix systems may prove useful in allocation of budgets and therefore should be investigated further when examining prescribing patterns in general practices in the UK, particularly for specific therapeutic areas.

INTRODUCTION

Prescribing by general practitioners costs around £7.8bn (€9.9bn; $15.3bn) a year, about 10% of the National Health Service's expenditure in England.[1] General practitioners' prescribing is coming under increasing scrutiny, with considerable pressure to prescribe cost effectively.[2] Prescribing budgets for primary care trusts are now allocated using a needs based formula, yet allocation is largely based on historical prescribing patterns.[3]

Some primary care trusts are now using needs based models to determine prescribing budgets for general practices. These models are, however, largely based on the demographic profile of a practice population, sometimes with a weighting for local characteristics and do not generally contain any direct measure of morbidity within a practice. Consequently, general practices with higher burdens of morbidity may be unfairly scrutinised or penalised for high prescribing rates. We used the Johns Hopkins adjusted clinical group case mix system[4] to investigate how well patient level morbidity based measures of case mix explain the variability in prescribing among general practices in the UK.

METHODS

We obtained data from the UK General Practice Research Database.[5] Although prescriptions issued by specialists are not picked up in the database, most prescriptions for chronic disease are issued by general practitioners. Data for 2001 were obtained only for practices that met the "up to standard criteria" for the database (see bmj.com).[6]

We used the Johns Hopkins adjusted clinical group system software[7] to assign patients into one of 81 mutually exclusive Johns Hopkins adjusted clinical groups, on the basis of age, sex, and a combination of recorded diagnoses over a one year period. We then assembled these groups into six mutually exclusive categories using the range of diagnoses pertaining to each patient. These categories are constructed according to patients' expected resource use on the basis of a nationally representative database of 2 million US patients aged less than 65. We used these groups to represent patient morbidity, from group 1 (healthiest) to group 6 (sickest). The age groups were children (0-15 years), young adults (16-34), older adults (35-64), and adults of pensionable age (≥65).

Statistical analysis

We used a two level Poisson model with random intercepts to investigate the association between age, sex, morbidity, and number of prescriptions issued[8] (outcome and predictors were considered at the patient level), after accounting for clustering within the general practices.

Initially we estimated the extent of variation in prescribing at the practice level that is explained by the predictors, using an adjusted R^2 measure based on a linear regression model.[9] To partition the variation in prescribing at practice and patient levels we used an R^2 measure derived from a two level logistic regression with random intercepts.[10] For this purpose we converted the number of prescriptions to a dichotomous response according to whether or not a patient had received a prescription. We carried out a sensitivity analysis to check the consistency of the results using another type of R^2 measure estimated from a two level linear regression model with random intercepts.[10] We used a square root transformation of the number of prescriptions issued as the response to satisfy the

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008;337;a238.

assumptions of normality. We compared the R^2 measures obtained from all three methods across models fitted with no predictors; age and sex; and age, sex, and morbidity. We used residual plots to investigate assumptions of normality of residuals required by the multilevel models.

RESULTS

One hundred and twenty nine practices with 1 032 072 patients were eligible. The median time that a patient had been registered with a general practitioner in 2001 was 11 years. Overall, 64% of patients were issued a prescription at least once during 2001. The median percentage of patients issued a prescription by the practices was 65% (90% range 11% to 75%). Across the 129 practices the median number of prescriptions issued to a patient was 2 (0 to 18) and the median total number of prescriptions issued was 9852 (3508 to 14 589).

The number of patients in the two sickest morbidity groups was small and therefore combined. The sex distribution of patients was similar across the practices (see bmj.com). The age and morbidity distributions of patients varied, however, particularly for those in the elderly group (≥65 years) and for morbidity groups 4-6. The median number of prescriptions issued increased with age and morbidity and was higher for females. The number of prescriptions issued by the practices varied, with the highest variation occurring in the oldest age group and in morbidity groups 5 and 6. The number of prescriptions issued to a patient was strongly associated with age and morbidity (table), increasing steeply with age and morbidity.

Morbidity explained more of the total variability than patients' age and sex alone (80% *v* 10%; see bmj.com). Of the total variation, 0.1% remained unexplained at the practice level and 19% remained unexplained at the patient level, after adjusting for age, sex, and morbidity. When adjusting for only age and sex the values were 4% and 86%. Most (96%) of the total variation was within practices. The extent of variation explained based on the sensitivity analysis was 60% at patient level and 74% at practice level when morbidity was included and 20% and 6% when only age and sex were included. These results were supported by the practice level analysis (see bmj.com).

Association between age, sex, and morbidity and number of prescriptions issued (results from two level Poisson regression models using patient level data)

Variable	Rate ratio (95% CI)	
	Model 2*	Model 3†
Age group (years):		
0-15	1	1
16-34	1.26 (1.25 to 1.26)	1.13 (1.12 to 1.13)
35-64	2.26 (2.25 to 2.27)	1.85 (1.84 to 1.86)
≥65	5.65 (5.63 to 5.67)	3.38 (3.37 to 3.39)
Sex:		
Male	1	1
Female	1.38 (1.37 to 1.38)	1.10 (1.10 to 1.11)
Morbidity:		
1 (healthiest)	—	1
2	—	43.42 (42.83 to 44.02)
3	—	58.21 (57.53 to 58.89)
4	—	97.03 (95.89 to 98.18)
5 and 6 (sickest)	—	134.56 (132.73 to 136.42)

Number of prescriptions issued for each patient was considered as response variable.
*Age and sex.
†Age, sex, and morbidity.

DISCUSSION

Patient morbidity explains more of the variability in prescribing than patients' age and sex. About 4% of the total variation is at the practice level and most is within practices.

Studies have shown that prescribing in general practice varies considerably. Statistical models from these studies have not included direct measures of case mix and have generally explained only a small proportion of this variation. Other than morbidity within a practice other factors that could influence prescribing include deprivation; doctors' knowledge, experience, role perception, and time pressures; the number of doctors in the practice; and patients' expectations of receiving a prescription and their demands.

We used data from the General Practice Research Database, which has been shown to be of high quality. The practices submitting information to the database are reasonably representative of the age and sex profile of the UK population, with some under-representation of inner city practices. The average size of the practices is greater than the national average.[11 12] In contrast with many studies of variation in prescribing, this study used data at patient level rather than an ecological design which has the limitation of drawing inferences at the individual patient level solely on the basis of aggregate statistics. We also controlled for diagnosis based morbidity groupings designed for use in primary care when examining variation in prescribing. Although the adjusted clinical group system was developed for use in the United States, it has been used in several UK based studies. Finally, the adjusted clinical group system depends on diagnostic codes recorded by the doctors during consultations and therefore may vary.

This study used patients' clinical case mix based on morbidity to explain variation in prescribing between general practices. Morbidity helped explain the variation in prescribing and in determining which patient groups are most likely to receive prescriptions. A model including morbidity has therefore potential utility for monitoring prescribing and the allocation of prescribing budgets.

Conclusions

Inclusion of a diagnosis based patient morbidity measure into prescribing models can explain a large amount of variability at patient and practice levels. The use of patient based case mix systems should be explored further when examining variation in prescribing patterns between practices in the UK, in particular for prescribing volume and for specific therapeutic categories. Case mix systems may prove useful in fairer allocation of budgets

WHAT IS ALREADY KNOWN ON THIS TOPIC

Prescribing by UK doctors is under increased scrutiny, with pressure to prescribe cost effectively

Studies have not explained well the large difference in prescribing rates between practices

WHAT THIS STUDY ADDS

Inclusion of a diagnosis based patient morbidity measure in prescribing models can explain a large amount of variability, both between and within practices

Patient based case mix systems may help in the allocation of budgets

and in the production of case mix adjusted measures of performance.

Contributors: See bmj.com.
Funding: The statistical analysis was partially supported by a primary care researcher award from the Department of Health. The work was undertaken at University College London Hospital/University College London, which received a proportion of funding from the Department of Health's National Institute of Health Research Biomedical Research Centres funding scheme. The Department of Primary Care and Social Medicine at Imperial College is supported by the National Institute of Health Research Biomedical Research Centre scheme.
Competing interests: None declared.
Ethical approval: This study was approved by the scientific and ethical advisory committee, responsible for the Medicines and Healthcare products Regulatory Agency General Practice Research Database.
Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 30 April 2008

Role of co-trimoxazole prophylaxis in reducing mortality in HIV infected adults being treated for tuberculosis: randomised clinical trial

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Cite this as: *BMJ* 2008;337:a257
doi:10.1136/bmj.a257

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2008;337:a257

ABSTRACT

Objective To assess the impact of prophylactic oral co-trimoxazole in reducing mortality in HIV positive Zambian adults being treated for pulmonary tuberculosis.
Design Double blind placebo controlled randomised clinical trial.
Participants Two groups of antiretroviral treatment naive adults with HIV infection: patients newly diagnosed as having tuberculosis and receiving tuberculosis treatment either for the first time or for retreatment after relapse; previously treated patients not receiving treatment.
Intervention Oral co-trimoxazole or matching placebo daily.
Primary outcome measures Time to death and occurrence of serious adverse events related to study drug.
Results 1003 patients were randomised: 835 (416 co-trimoxazole, 419 placebo) were receiving treatment for tuberculosis, 762 (376 co-trimoxazole, 386 placebo) of them newly diagnosed previously untreated patients and 73 (40 co-trimoxazole, 33 placebo) receiving a retreatment regimen; 168 (84 co-trimoxazole, 84 placebo) were not on treatment but had received treatment in the past. Of 835 participants receiving tuberculosis treatment, follow-up information was available for 757, with a total of 1012.6 person years of follow-up. A total of 310 (147 co-trimoxazole, 163 placebo) participants died, corresponding to death rates of 27.3 and 34.4 per 100 person years. In the Cox regression analysis, the hazard ratio for death (co-trimoxazole:placebo) was 0.79 (95% confidence interval 0.63 to 0.99). The effect of co-trimoxazole waned with time, possibly owing to falling adherence levels; in a per protocol analysis based on patients who spent at least 90% of their time at risk supplied with study drug, the hazard ratio was 0.65 (0.45 to 0.93).
Conclusions Prophylaxis with co-trimoxazole reduces mortality in HIV infected adults with pulmonary tuberculosis. Co-trimoxazole was generally safe and well tolerated.
Trial registration Current Controlled Trials ISRCTN15281875.

INTRODUCTION

A provisional recommendation was made by the World Health Organization and the Joint United Nations Programme on HIV/AIDS (UNAIDS) in

2000 that co-trimoxazole should be given to all adults and children in Africa with symptomatic HIV-1 infection.[1] This followed the conclusions of trials in Côte d'Ivoire.[2 3] A small randomised clinical trial from Senegal was stopped early (because of the announcement of the WHO/UNAIDS recommendations[1]); the authors concluded that chemoprophylaxis with low dose co-trimoxazole did not show a beneficial effect on survival or the occurrence of opportunistic or non-opportunistic infections.[4] The levels of resistance of locally relevant pathogens to co-trimoxazole was low in the Côte d'Ivoire studies, whereas much higher rates have been reported elsewhere.

In Zambia, after careful consideration of the evidence, three randomised placebo controlled clinical trials of co-trimoxazole prophylaxis were agreed to: in children with HIV[5]; in postnatal women with HIV; and in adults with HIV and tuberculosis, which is reported here.

METHODS

Study setting, population, and intervention

We enrolled two groups of HIV positive, antiretroviral naive Zambian adults aged 16-60 years from the University Teaching Hospital chest clinic in Lusaka and randomised them to receive daily co-trimoxazole or matching placebo for the duration of the trial. The two groups were newly diagnosed, previously untreated patients with smear positive pulmonary tuberculosis receiving antituberculosis treatment (after one year, patients receiving a retreatment regimen were also eligible) and clinically healthy people previously treated for tuberculosis but no longer receiving any treatment.

Eligible patients were randomised in a 1:1 ratio to receive a supply of pre-labelled trial drug (co-trimoxazole or matching placebo; two tablets to be taken daily). Both patients and staff working on the trial in Zambia were blind to the allocation. We issued participants with a container of study drug bearing their trial number with instructions about taking the tablets and an appointment date four weeks later.

Treatment for tuberculosis and opportunistic infections

We followed national tuberculosis treatment guidelines for patients with active, previously untreated tuberculosis. Patients who needed re-treatment for relapse received one of the WHO recommended retreatment regimens.

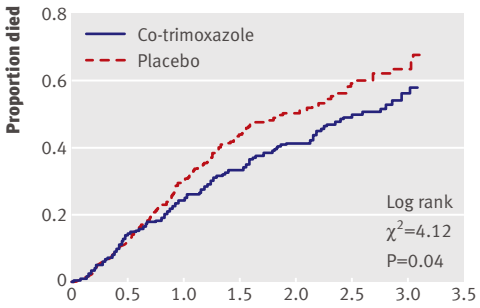
If participants developed any illnesses requiring the use of co-trimoxazole, we discontinued the study drug and administered open label co-trimoxazole. The trial drug was then resumed after treatment.

Outcomes

The primary end points were all cause mortality and adverse events leading to an interruption of trial drug.

Follow-up

We saw participants every four weeks up to 16 weeks and every eight weeks thereafter until the close of the trial. We recorded details of possible adverse drug effects. When participants failed to attend an outpatient appointment their names were carried forward to the next week of the diary after which the home visitor team made efforts to find them. We collected clinical specimens for microbial analysis from participants who reported ill with symptoms and signs. When bacteria were cultured, we tested them for sensitivity to antibiotics.



At risk:				
Co-trimoxazole	416	219	108	33
Placebo	419	190	79	17

Time to death according to trial drug (based on 835 HIV positive patients newly diagnosed as having, and being treated for, tuberculosis)

Sample size and data analysis

From our sample size calculation, we needed 1408 person years of observation to show a 35% reduction in death rate in patients receiving co-trimoxazole, at the 5% level of significance with 80% power; a 40% reduction would require 1045 person years.

We used the Kaplan-Meier method, the log rank test, and a Cox proportional hazard regression model to make comparisons of the groups for the primary end point by time to event analyses and tested heterogeneity of survival rates in subgroups by interaction tests within Cox models.

RESULTS

Participant flow

Of 1505 people who were known to be HIV positive, we randomised 1003 between June 2000 and January 2004 (see bmj.com). Of these, 835 (416 co-trimoxazole, 419 placebo) were receiving treatment for tuberculosis, of whom 762 (376 co-trimoxazole, 386 placebo) were newly diagnosed previously untreated patients and 73 (40 co-trimoxazole, 33 placebo) were receiving a retreatment regimen; 168 (84 co-trimoxazole, 84 placebo) were not on treatment but had received treatment in the past. The trial was closed in September 2004, when funding for antiretroviral treatment became available for those participants who were eligible. Follow-up from the time of randomisation ranged from 0 to 46 months. A total of 1012.6 person years of data were accumulated from participants receiving treatment for tuberculosis at the time of randomisation (919.2 from newly diagnosed previously untreated patients and 93.4 from those being retreated for relapse) and 457.5 person years from those not on treatment. The main analyses are restricted to patients receiving antituberculosis treatment.

Baseline data

The two groups were broadly similar in their characteristics at baseline (see bmj.com). Apart from symptoms associated with tuberculosis, only a small number of participants had symptoms associated with HIV/AIDS. Only 348 (42%) of the participants had CD4 counts (measured no later than two weeks after the start of trial drug); 55% of these had counts less than 200 cells/μl.

Follow-up

We had no information on 78 (37 co-trimoxazole, 41 placebo) (9.3%) participants after randomisation. Follow-up rates were slightly higher in the co-trimoxazole arm than in the placebo arm throughout the study. The proportion seen or known to have died remained at 80% or more throughout the study. During follow-up, participants in the co-trimoxazole group received trial drug during 82.9% of their time at risk and those in the placebo group received trial drug 81.0% of that time. Of those participants seen at follow-up, 269/379 (71%) in the co-trimoxazole group and 259/378 (69%) in the placebo group spent 80% or more of their time supplied with trial drug; the corresponding proportions who spent 90% or more of their time supplied with drug were 204/379 (54%) and 201/378 (53%).

Outcomes and death rates in patients on tuberculosis treatment

A total of 310 patients died during the course of the study (table). Co-trimoxazole was associated with a 21% reduction in all cause mortality (hazard ratio 0.79, 95% confidence interval 0.63 to 0.99; P=0.04). The number needed to treat to prevent one death was 141.8 (95% confidence interval 71.7 to 588.7). The figure shows the Kaplan-Meier plots of time to death for all 835 patients. The figure suggests a delay before any benefit from co-trimoxazole becomes evident (see exploratory analyses below). We saw benefit in both newly diagnosed, previously untreated participants and in those being treated for relapse. Analysis by CD4 count on the subset of participants with data available showed no evidence of difference in benefit according to the level of immunosuppression (P>0.5, test for heterogeneity); we saw no difference in benefit by age or sex.

Ancillary and exploratory analyses

We explored possible changes in the effect of co-trimoxazole over a prolonged period of time by dividing time after randomisation into four segments —0-6, 6-12, 12-18, and ≥18 months—in a retrospective analysis of newly diagnosed, previously untreated patients. We found significant differences in the different time periods (P=0.02, test for heterogeneity), with no evidence of benefit in the first six months but a consistent benefit between six and 18 months associated with a 45% reduction in mortality in participants receiving co-trimoxazole. From 18 months onwards, no further benefit was apparent. Fitting a fractional polynomial to the effect of randomised group over time and shrinking the effect of outliers beyond three years confirmed these results, although the confidence limits were wide.

Unplanned analyses suggested that benefit from co-trimoxazole was associated with the proportion of time at risk for which participants were in receipt of trial drug. Thus, for those spending 90% or more, 75%-90%, or less than 75% of their time supplied with study drug, the hazard ratios were 0.65 (0.45 to 0.93), 0.68 (0.40 to 1.18), and 1.24 (0.88 to 1.73).

Adverse events leading to planned interruption of trial drug

Suspected adverse events leading to a planned interruption of trial drug occurred in 18 patients (12 co-trimoxazole, 6 placebo). All except six (all co-trimoxazole) resumed the trial drug.

Death rates in previously treated patients not on treatment at time of enrolment

The death rates in the 168 patients who had received treatment for tuberculosis in the past but were not on treatment at the time of enrolment were 14.5 (95% confidence interval 10.3 to 20.5) per 100 person years in the placebo arm and 14.7 (10.5 to 20.6) per 100 in the co-trimoxazole arm.

Death rates by tuberculosis disease status and trial drug (HIV positive patients newly diagnosed as having, and being treated for, tuberculosis)

Tuberculosis category and trial drug	Patients assessed	Person years	Deaths	Rate (95% CI) per 100 person years
All patients receiving tuberculosis treatment:				
Co-trimoxazole	416	538.3	147	27.3 (23.2 to 32.1)
Placebo	419	474.3	163	34.4 (29.5 to 40.1)
Newly diagnosed, previously untreated:				
Co-trimoxazole	376	479.4	135	28.2 (23.8 to 33.3)
Placebo	386	439.8	149	33.9 (28.9 to 39.8)
Relapse/retreatment:				
Co-trimoxazole	40	58.9	12	20.4 (11.6 to 35.8)
Placebo	33	34.5	14	40.6 (24.0 to 68.5)

WHAT IS ALREADY KNOWN ON THIS TOPIC

HIV positive patients with active tuberculosis have a high risk of death because of increased susceptibility to bacterial infections

Two clinical trials from Cote d'Ivoire showed that co-trimoxazole prophylaxis reduced mortality in these patients, whereas one trial from Senegal showed no effect

The findings of the west African trials might not extend to other parts of the world where levels of resistance to co-trimoxazole are high

WHAT THIS STUDY ADDS

Prophylaxis with co-trimoxazole reduced mortality in HIV positive adults with pulmonary tuberculosis in Zambia, an area with high levels of bacterial resistance

The results support UNAIDS/WHO recommendations made in 2000

DISCUSSION

This study confirms the results of the trial done in Côte d'Ivoire and the subsequent observational studies, in showing that prophylaxis with co-trimoxazole reduces mortality in adults with HIV infection who have pulmonary tuberculosis and that co-trimoxazole was generally safe and well tolerated. This is the only placebo controlled randomised clinical trial of co-trimoxazole prophylaxis that we are aware of in HIV positive adults with active tuberculosis since those done in Côte d'Ivoire and Senegal.[2 4]

Several non-randomised studies have been reported from central and southern Africa,[6-9] which all found lower mortality in the group treated with co-trimoxazole than in the comparison group. These studies all have potential limitations (see bmj.com).

Overall, the reduction in risk found in our study was less than has been reported elsewhere. Retrospective exploratory analyses in the newly diagnosed patients indicate a lack of benefit during the first six months, coinciding in part with the administration of rifampicin (which has a broad spectrum of activity against a variety of bacterial infections) in the initial two month intensive phase of their antituberculosis chemotherapy. After this came a period of about 12 months during which we saw a significant reduction in mortality of 45%, very similar to those reported in the Cote d'Ivoire trial and the CHAP trial of HIV positive children in Zambia.[2 5] These results should be interpreted with caution, as they are based on unplanned subgroup analyses with relatively small numbers of person years. However, the benefit seems to wane in the long term, possibly owing to a fall in adherence levels, development of resistance to co-trimoxazole, or death from causes not prevented by co-trimoxazole. An analysis according to time in receipt of study drug showed a significant benefit in patients who collected co-trimoxazole regularly.

Our findings now provide a strengthened evidence base for the UNAIDS /WHO guidelines issued in 2000.[1] The WHO Department of HIV/AIDS has recently revised the interim UNAIDS/WHO policy on use of co-trimoxazole in people living with HIV/AIDS.[10] Analysis by CD4 counts on the subset of participants with data available showed no differences in benefit according to level of immunosuppression. Limited data on CD4 counts suggest no clear evidence as to when to start co-trimoxazole. The optimal timing of co-trimoxazole prophylaxis has yet to be determined.

We thank the study participants, the study team members, UTH Chest Clinic staff, the Data Monitoring Committee (Tim Peto, Godfrey Biemba, Maria Quigley, and Mike Sharland), Charles Gilks for assistance with study design, the Zambian Ministry of Health national tuberculosis and leprosy control programme and the UTH Board of Management for their encouragement and support, Sarah Walker who did the exploratory analyses, and Diana Gibb of the MRC CTU for helpful comments.

Contributors: See bmj.com

Funding: Health and Population Division, UK Department for International Development (project grant LUCOT). The study was done under the auspices of the University of Zambia, University College London (UNZA-UCLMS) Research and Training Project. The funding sponsor of the study had no role in the conception or design of the study; the collection, analysis, or interpretation of the data; or the drafting and writing of the manuscript.

Competing interests: None declared.

Ethical approval: University of Zambia research ethics committee and the joint UCL/UCLH committees on the ethics of human research, University College London.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 9 May 2008

Patients' refusal to consent to storage and use of samples in Swedish biobanks: cross sectional study

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Cite this as: *BMJ* 2008;337:a345
doi:10.1136/bmj.a345

ABSTRACT

Objectives To estimate how many people object to storage of biological samples collected in health care in Sweden and to their use in research and how many withdraw previous consent.

Design Cross sectional study of register data.

Setting Biobanks used in Swedish health care, 2005-6.

Population Data on refusal to consent were obtained for 1.4 million biobank samples per year from 20 of 21 counties.

Main outcome measures Rates of preliminary refusal to consent, confirmed refusal, and withdrawal of consent.

Results Patients refused consent to either storage or use of their samples in about 1 in 690 cases; about 1 in 1600 confirmed their decision by completing a dissent form. Rather than having the samples destroyed, about 1 in 6200 patients wanted to restrict their use. Of those who had previously consented, about 1 in 19 000 withdrew their consent.

Conclusions Refusal to consent to biobank research in Sweden is rare, and the interests of individuals and research interests need not be at odds. The Swedish healthcare organisation is currently obliged to obtain either consent or refusal to each potential use of each sample taken, and lack of consent to research is used as the default position. A system of presumed consent with straightforward opt out would correspond with people's attitudes, as expressed in their actions, towards biobank research.

INTRODUCTION

Erosion of trust[1-3] in health care and medical science could have severe consequences for medical research.[4-6] Some studies, however, do not support these concerns.[4 7-10] A recent overview of international surveys found that at least 80% of people are willing to donate biological material for research.[11] Willingness might be even higher in Sweden.[12-14] Most Swedes seem to prefer general, one time consent in this context.[5 15] People might be less concerned in their daily life about risks entailed by biobank research than they claim to be in surveys.

We determined the extent to which Swedish patients refused consent to storage or restricted the use of samples taken in public health care in 2005 and 2006; whether this poses an actual threat to biobank research; and whether trust in biobank research associated with Swedish health care is eroding.

METHODS

Our targets were biobanks used in health care across the country. We did not include biobanks used exclusively for research or material from blood donations, autopsies, and fetal and infant screening.

Patients can express preliminary refusal to consent either when samples are taken or later by contacting the county's biobank coordinator. In either case, refusal must be confirmed by submitting a "dissent form" specifying the nature of the refusal (to storage, research, or some particular use). We asked biobank registers across the country for data on confirmed refusal toconsentand the number of laboratory referrals, which is equal to or less than the number of samples, in 2005 and 2006. We obtained full data for 13 of 21 counties, and partial coverage for seven; one county was unable to comply with the request.

Data were separated into series by sample type (for example, histopathological biopsies and cervical screening smears) and geographical location.

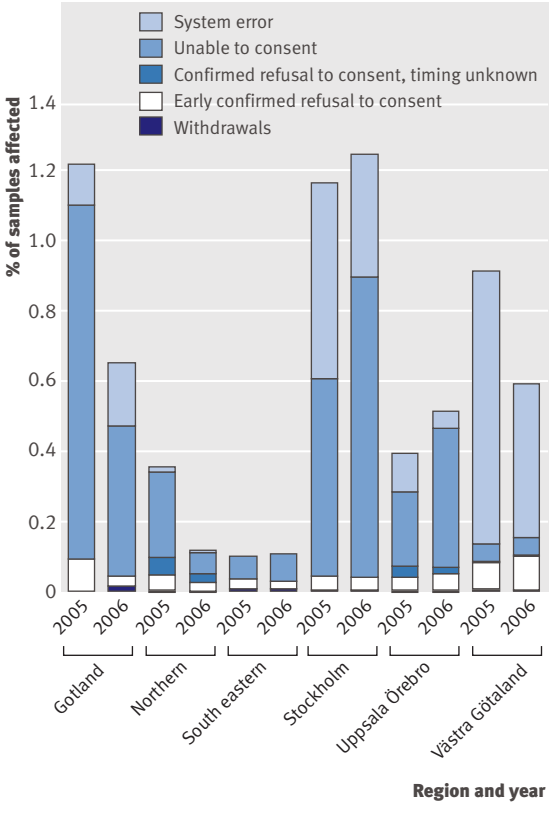

Fig 1 | Data from all 83 series per year. Not every series had data on system errors and inability to consent; missing values have been extrapolated. Not all registers specified whether patients refused consent early or late, so some withdrawals might be hidden in the "timing unknown" category

This article was published on bmj.com. Cite this as: *BMJ* 2008;337:a345

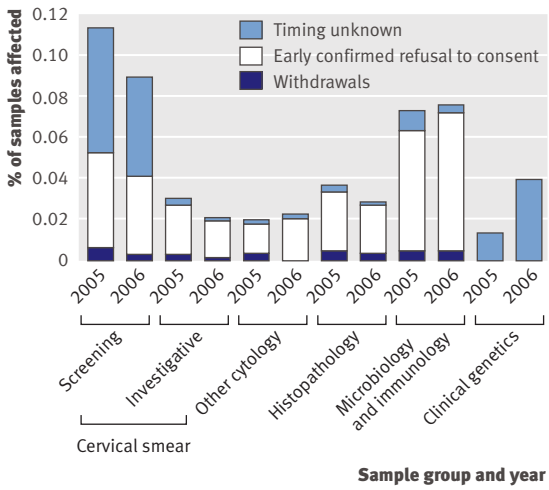

Fig 2 | Data from 73 series per year that contained single, predefined sample types. Patients most likely to refuse consent were women undergoing screening for precancerous changes in cervix. In the clinical genetics category, interpretation is difficult because of small number of referrals (<8000/year); in absolute numbers, bars represent one and three cases of dissent, respectively. Other categories are larger (from 48 000 to >500 000 samples/year)

Variables were expressed as percentages of the number of referrals. For each calculation, we excluded those and only those sample series for which the numerator was missing. We detected changes in overall ratios over time with χ^2 test with continuity correction. We did not test for differences series by series, because they varied almost 700-fold in size.

RESULTS

During 2005-6, about 1 in 690 potential donors expressed preliminary refusal to consent. Of these, about half confirmed their decision. A quarter of those who confirmed their refusal wanted to restrict the use of samples rather than having them destroyed, and 1 in 19 000 patients who initially consented withdrew their consent. The table summarises the main findings .

The main causes of "drop out" from future research (fig 1) were inability to consent (0.25%) and system errors (0.26%); the former increased (from 0.20% to 0.29%, P<0.001) from 2005 to 2006, while the latter dropped dramatically (from 0.33% to 0.19%, P<0.001) (table). Differences between regions can be explained by variations in follow-up practices and errors in reporting (for example, using the "inability to consent" category for indecisive patients or use of obsolete referral forms). Between sample types, refusal to consent was most common in the cervical screening subgroup (0.10%; fig 2).

Preliminary rates of refusal to consent were particularly high in one pathology laboratory (794/207 866 (0.38%) in 2005 and 902/210 980 (0.43%) in 2006); however, only a tenth of these patients confirmed their decisions. Regarding confirmed refusal, we identified extreme outliers in two small series of seminal fluid samples (8/307 (2.6%) in 2005 and 8/403 (1.9%) in 2006).

DISCUSSION

Fewer than 700 in one million Swedes actively oppose storage of or research using biobank samples collected in routine health care. Most of them refuse consent to storage, which is consistent with previous findings that privacy is important whereas the purpose of research is a lesser concern.[11 15 16] The threat posed to quality of research is arguably minimal.

We believe that our results, although not necessarily generalisable to other contexts or cultures, are representative of patients in Sweden. The geographic coverage was sufficient. The age distribution might be skewed as elderly people are more frequent consumers of health care. Even among young to middle aged women in the cervical screening subgroup, however, the rates of refusal to consent were only about 0.1%.

Refusal to consent to storage and use of biobank samples in Sweden in 2005 and 2006

	Sample series included*	2005			2006		
		Rate	Rate in % (95% CI)	IQR for rate	Rate	Rate in % (95% CI)	IQR for rate
Preliminary refusal to consent	72	1656/1 191 176	0.139 (0.132 to 0.146)	0.031-0.123	1806/1 208 717	0.149 (0.143 to 0.156)	0.022-0.097
Confirmed refusal to consent	83	954/1 442 998	0.066 (0.062 to 0.070)	0.000-0.075	888/1 466 659	0.061 (0.057 to 0.065)	0.007-0.056
Specific refusal to consent	79	224/1 401 572	0.016 (0.014 to 0.018)	0.000-0.019	234/1 424 517	0.016 (0.014 to 0.019)	0.000-0.017
Withdrawal of consent	69	66/1 168 634	0.0056 (0.0043 to 0.0070)	0.0000-0.0061	58/1 194 676	0.0049 (0.0036 to 0.0061)	0.0000-0.0049
Unable to consent	73	2469/1 218 372	0.20 (0.19 to 0.21)	0.00-0.23	3639/1 239 765	0.29 (0.28 to 0.30)	0.00-0.09
System error	74	4049/1 213 496	0.33 (0.32 to 0.34)	0.00-0.02	2376/1 236 391	0.19 (0.18 to 0.20)	0.00-0.00

IQR=interquartile range.
*Not all 83 sample series (groups of samples by type and geographical location) had data for each variable. Several rates fall outside corresponding interquartile ranges, which reflects presence of influential outliers.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The right of patients to refuse consent to the use of their biological samples in research, and the right to withdraw previous consent, could harm quality of research

The threat could be even greater if trust in medical research and health care is eroding

WHAT THIS STUDY ADDS

During 2005 and 2006 in Sweden, for 1.4 million samples the rate of confirmed refusal to consent was 1 in 1600 for storage or use in research, and 1 in 19 000 people withdrew previous consent

These figures suggest no immediate threat to biobank research and no crisis of trust in research

One concern has been that refusal to consentcould be underestimated if several samples requiring separate referrals are taken in one session but the patient submits only one form to cover them all. While such a distortion might affect serological examinations, it is probably less pronounced for the other sample types.

Many people are unfamiliar with biobanks and might be underinformed about their rights and the possible implications of storing biological material. Still, people are becoming increasingly well informed through other channels, such as television, newspapers, the internet, and posters in waiting rooms. If people were concerned about their samples, we would expect more of them to refuse consent over time. Because of the short time frame our results do not exclude the possibility of such a trend, but neither do they support it.

Trust in health care and research

While our results tell us what patients do, they may indicate little of what they think. Surveys based on hypothetical situations, though with problems of their own,[17 18] might provide more reliable measures of trust. On the other hand, if we believe that there is a connection between attitudes of trust and trusting behaviour, and, more particularly, assuming that most people with deeply felt distrust will not, given the choice, place trust,[19] our results give us no reason to believe that distrust is widespread.

A complex and costly administration has been set up to protect the small minority of patients who do not want their samples to be stored in biobanks or used in research. The right to say "no" might be justified, no matter how small the minority utilising it,[20] but the means chosen to protect it seem flawed. A system that consumes resources from public health care[21] and imposes a bureaucracy with no benefits, while possibly still failing to inform people of their rights, is not likely to evoke the trust so urgently needed.[22] Though informed consent in biobank research is a complex issue[23] that warrants further research, the present study gives some reasons to consider an alternative system, where consent would be presumed, information readily available, and opting out straightforward.

This study was conducted as part of the AutoCure project of the EU Sixth Framework Programme.
Contributors: LJ collected and analysed data and wrote the paper. All authors contributed equally to study design and revision of critical intellectual content and approved the final version. LJ is guarantor.
Funding: AutoCure project within the EU Sixth Framework Programme.
Competing interests: None declared.
Ethical approval: Not required.
Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 8 May 2008