# Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland

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## Abstract

***Objectives*—To estimate the extent to which changes in the main coronary risk factors (serum cholesterol concentration, blood pressure, and smoking) explain the decline in mortality from ischaemic heart disease and to evaluate the relative importance of change in each of these risk factors.**

***Design*—Predicted changes in ischaemic heart disease mortality were calculated by a logistic regression model using the risk factor levels assessed by cross sectional population surveys, in 1972, 1977, 1982, 1987, and 1992. These predicted changes were compared with observed changes in mortality statistics.**

***Setting*—North Karelia and Kuopio provinces, Finland.**

***Subjects*—14257 men and 14786 women aged 30-59 randomly selected from the national population register.**

***Main outcome measures*—Levels of the risk factors and predicted and observed changes in mortality from ischaemic heart disease.**

***Results*—The observed changes in the risk factors in the population from 1972 to 1992 predicted a decline in mortality from ischaemic heart disease of 44% (95% confidence interval 37% to 50%) in men and 49% (37% to 59%) in women. The observed decline was 55% (51% to 58%) and 68% (61 to 74) respectively.**

***Conclusion*—An assessment of the data on the risk factors for ischaemic heart disease and mortality suggests that most of the decline in mortality from ischaemic heart disease can be explained by changes in the three main coronary risk factors.**

## Introduction

Mortality from ischaemic heart disease is decreasing in many countries although increasing in many others.[1] To what extent changes in the important risk factors—raised serum cholesterol concentration, raised blood pressure, and smoking—explain the trends in mortality from ischaemic heart disease is an important public health question. Most industrialised countries are developing and adopting national strategies to prevent ischaemic heart disease, mainy by reducing the levels of these known risk factors in the population.

Only a few studies have estimated the extent to which the changes in risk factors explain the decline in mortality from ischaemic heart disease.[2,3] The lack of such studies reflects the fact that either few data have been available or data have been insufficient to permit proper analysis of this issue. Finland has been one of the most active countries in developing and testing preventive measures for cardiovascular disease. In the early 1970s middle aged Finnish men had the highest mortality from cardiovascular disease in the world.[4]

We aimed to analyse the extent to which the changes in the main coronary risk factors explain the decline in mortality from ischaemic heart disease and to evaluate the relative importance of change in each of these risk factors. We could do this because mortality statistics, surveys of risk factors, and cohort studies provided the necessary standardised data for a clearly defined population over 20 years.

## Subjects and methods

Five cross sectional population surveys, in 1972, 1977, 1982, 1987, and 1992, assessed the levels of coronary risk factors in the provinces of North Karelia and Kuopio. For each survey a random sample for each province was drawn from the national population register. In 1972 and 1977 each sample was 6·6% of the population born during 1913-47. In 1982, 1987, and 1992 the samples comprised people aged 25-64. The samples were stratified so that at least 250 subjects of each sex and 10 year age group (25-34, 35-44, 45-54, and 55-64) were chosen in each area. The common age range in all the five surveys was 30-59, which is the age range for the data on risk factors that we used in this study.

In 1982, 1987, and 1992 we followed the protocol established by the MONICA project (an international study conducted under the auspices of the World Health Organisation to monitor trends in and determinants of mortality from cardiovascular disease).[5] This protocol was similar to the methods used in 1972 and 1977. Subjects completed a self administered questionnaire, which covered mainly questions on socioeconomic factors, medical history, current health, and psychosocial factors. Specially trained nurses measured the subjects' height, weight, and blood pressure and took venous blood specimens to determine the serum cholesterol concentration. Each survey followed the same methods as closely as possible, and both provinces were treated in the same way—for example, the blood samples were not analysed consecutively. Blood pressure was measured once from the right arm of each subject after he or she had been seated for five minutes. Phase V of the Korotkoff sounds was recorded as the diastolic pressure.

In 1972 and 1977 serum cholesterol concentrations were determined from frozen samples with the Liebermann-Burchard method, whereas in 1982, 1987, and 1992 they were determined from fresh samples with an enzymatic method (cholesterol oxidase-phenol aminophenazone peroxidase (CHOD-PAP)), Boehringer Mannheim; Monotest). All cholesterol concentrations were determined in the same central laboratory, which was standardised against national and international reference laboratories.

Smoking was assessed with a standard set of questions in the self administered questionnaire. On the basis of their responses the respondents were classified as smokers or non-smokers. Smokers were those who had smoked cigarettes, cigars, or a pipe regularly for at least one year and had smoked more than once a day on average during the preceding six months; non-smokers were those who had never smoked regularly and those who had smoked regularly but had stopped smoking at least six months before the start of the survey.

Table I shows the sample sizes and participation

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rates in the five surveys. Participation rates were high (>90%) in the 1972 survey; they decreased slightly in the later surveys but remained satisfactory.

TABLE I—*Sample size (percentage participation rate) by sex, year, and geographical area in subjects aged 30-59 who participated in five studies of levels of coronary risk factors in Finland*

| Year of study | North Karelia | | Kuopio Province | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| 1972 | 1959 (94) | 2056 (96) | 2918 (91) | 2949 (94) |
| 1977 | 2063 (87) | 2020 (91) | 2933 (89) | 2996 (92) |
| 1982 | 1599 (77) | 1511 (84) | 1459 (83) | 1143 (88) |
| 1987 | 1521 (79) | 1485 (87) | 762 (82) | 744 (87) |
| 1992 | 759 (69) | 750 (82) | 768 (76) | 735 (85) |

Deaths in which ischaemic heart disease (*International Classification of Diseases*, eighth revision (ICD-8), codes 410-414) was the underlying cause of death—according to the national mortality statistics—were linked to the survey cohort examined in 1972. Deaths that occurred during 1972-86 were included in the prospective follow up. We used death from ischaemic heart disease as the outcome variable in the logistic regression models. Analyses were done separately for men and women. Age, baseline total serum cholesterol concentration, and diastolic blood pressure were included as continuous variables and smoking status as a dichotomous variable. Socioeconomic factors (measured as years of education) and interactions among the risk factors were left out of the analysis because they were not significant in the logistic regression model after classic risk factors had been included in the model. Also, including years of education in the model had little effect on the odds ratios of the risk factors.

All these variables were available for 4243 men, of whom 303 had died of ischaemic heart disease, and for 4722 women, of whom 73 had died of ischaemic heart disease. The probability of death in the logistic regression model was for $1/(1+\exp(12{\cdot}73-0{\cdot}108\times\text{age}-0{\cdot}806\times\text{smoking}-0{\cdot}021\times\text{diastolic blood pressure}-0{\cdot}384\times\text{cholesterol}))$ for men and $1/(1+\exp(14{\cdot}90-0{\cdot}104\times\text{age}-1{\cdot}24\times\text{smoking}-0{\cdot}0306\times\text{diastolic blood pressure}-0{\cdot}365\times\text{cholesetrol}))$ for women. All terms were significant at a 0·001 risk level. We then calculated the average probability of a death from ischaemic heart disease for each year; the risk factor survey was done by including the mean risk factor values observed in the survey in this logistic regression function. The relative importance of each risk factor was estimated separately by changing in the logistic regression function the value of only that risk factor and keeping the other risk factors unchanged at the 1972 level. The percentage decline in predicted mortality from ischaemic heart disease compared with the 1972 mortality was then calculated for each survey year. We calculated the 95% confidence interval for this predicted decline by taking into account the standard errors of the risk factor level in each survey and the standard errors of the parameters' estimates in the logistic regression function.

Data on trends in mortality from ischaemic heart disease were obtained from the national mortality statistics for men and women aged 35-64. Yearly mortality was standardised for age in five year age groups, with the 1972 population in Finland as a standard population. The percentage decline in mortality from ischaemic heart disease was calculated with the mean of the years 1969-72 as the baseline. The 95% confidence interval for this observed decline was calculated on the basis of a Poisson distribution for the number of deaths in four baseline years and each survey year.

TABLE II—*Mean (standard error) level of coronary risk factors in subjects in Finland, by year and sex*

| Risk factors | 1972 | 1977 | 1982 | 1987 | 1992 |
|---|---|---|---|---|---|
| | | *Men* | | | |
| Cholesterol (mmol/l) | 6·78 (0·02) | 6·55 (0·02) | 6·28 (0·02) | 6·23 (0·03) | 5·90 (0·03) |
| Diastolic blood pressure (mm Hg) | 92·8 (0·18) | 91·0 (0·18) | 87·8 (0·26) | 88·4 (0·28) | 84·2 (0·37) |
| Smoking (% of study population who were smokers) | 53 (0·8) | 47 (0·8) | 42 (1·0) | 39 (1·2) | 37 (1·5) |
| | | *Women* | | | |
| Cholesterol (mmol/l) | 6·72 (0·02) | 6·36 (0·02) | 6·10 (0·03) | 5·94 (0·03) | 5·54 (0·03) |
| Diastolic blood pressure (mm Hg) | 91·8 (0·19) | 87·6 (0·17) | 84·6 (0·25) | 83·5 (0·26) | 79·6 (0·33) |
| Smoking (% of study population who were smokers) | 11 (0·5) | 12 (0·5) | 16 (0·8) | 16 (0·9) | 20 (1·1) |

## Results

From 1972 to 1992 total serum cholesterol concentrations decreased by 13·0% in men and 17·6% in women; diastolic blood pressure decreased by 9·2% in men and 13·3% in women. The prevalence of smoking decreased from 53% to 37% in men but increased from 11% to 20% in women (table II).

From 1969 to 1972 the mean age standardised mortality from ischaemic heart disease in men was 647/100 000 population, dropping to 289/100 000 in 1992. In women the corresponding decrease was from 114 to 36/100 000 (fig 1).

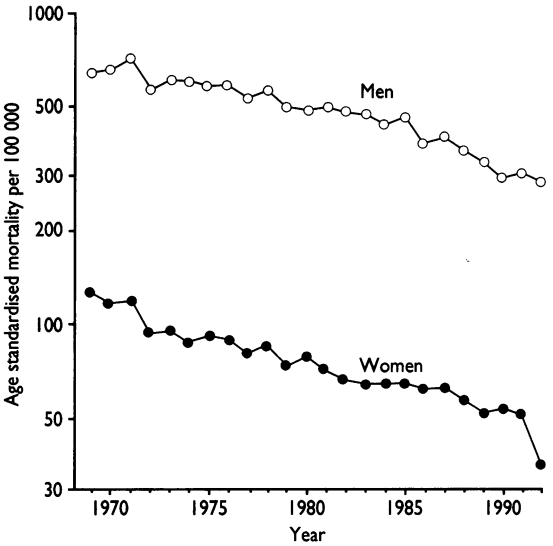


FIG 1—*Age standardised mortality from ischaemic heart disease from 1969 to 1992 in men and women aged 35-64 in Finland*

In men during 1972-92 the observed decline in mortality from ischaemic heart disease on the basis of the mortality statistics was 55% (95% confidence interval 51% to 58%) and the predicted decline in mortality on the basis of the logistic regression function and the observed changes in risk factors was 44% (37% to 50%) (fig 2). Until the mid-1980s the trend in observed mortality followed the predicted mortality, but after that the decline in observed mortality accelerated more than was predicted from the changes in risk factors. The 95% confidence intervals for the predicted decline in mortality included the observed decline until 1987 and 1992. The 95% confidence intervals for the observed and predicted declines in mortality from ischaemic heart disease did not overlap in 1992 (table III).

To estimate the relative importance of each risk factor we computed three additional models. In men the observed 13% decrease in serum cholesterol concentration predicted a 26% decline in mortality from ischaemic heart disease, the 9·2% decrease in diastolic blood pressure predicted a 15% decline, and the 16% decrease in smoking predicted a 10% decline. In women the observed mortality from ischaemic heart disease decreased by 68% during 1972-92 (fig 3). The predicted decrease, based on the changes in risk

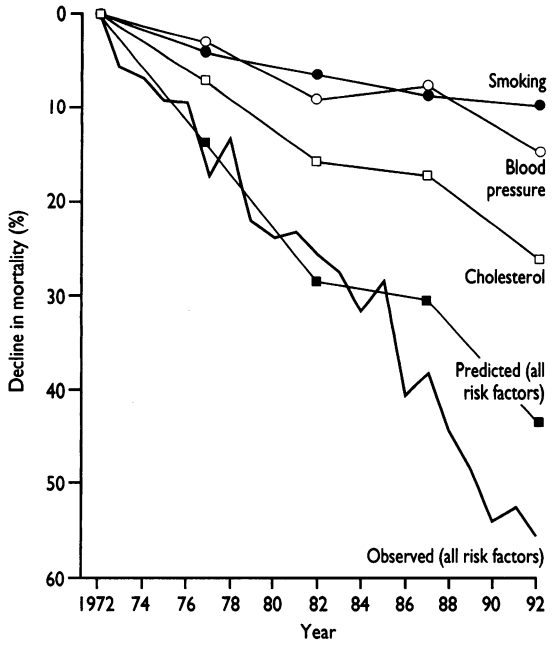


FIG 2—*Observed and predicted decline in mortality from ischaemic heart disease in men aged 35-64 in Finland*

TABLE III—*Percentage observed and predicted decline (95% (confidence interval)) in mortality from ischaemic heart disease in 1972-92 in men and women in Finland*

| | Decline in mortality | |
|---|---|---|
| | Observed | Predicted |
| | *Men* | |
| 1972 | | |
| 1977 | 17 (12 to 22) | 14 (10 to 17) |
| 1982 | 25 (20 to 30) | 28 (23 to 34) |
| 1987 | 38 (33 to 42) | 30 (25 to 36) |
| 1992 | 55 (51 to 58) | 44 (37 to 50) |
| | *Women* | |
| 1972 | | |
| 1977 | 28 (16 to 39) | 22 (14 to 29) |
| 1982 | 41 (31 to 51) | 32 (21 to 42) |
| 1987 | 45 (35 to 54) | 38 (25 to 48) |
| 1992 | 68 (61 to 74) | 49 (37 to 59) |

factors, was 49% (37% to 59%). In every survey year except 1992 the 95% confidence interval of the predicted mortality included the 95% confidence interval of the observed change (table III). The observed 18% decrease in cholesterol concentration predicted a 35% decline in mortality from ischaemic heart disease, the 13% decrease in diastolic blood pressure predicted a 31% decline, and the 9% increase in smoking predicted an 11% increase (fig 3).

## Discussion

The well standardised population surveys carried out every five years during the past 20 years and high quality mortality statistics in Finland enabled us to estimate the role of changes in risk factors in the observed decline in mortality from ischaemic heart disease. The results showed that we could predict about three quarters of this decline on the basis of changes in known risk factors in the population, both in men and in women. Almost half of the decline was associated with the decrease in serum cholesterol concentration.

Our results confirmed the estimate derived from clinical trials,[6] that a 1% decrease in cholesterol concentration leads to a 2% decline in risk of ischaemic heart disease. The appreciable decrease in cholesterol concentration is an obvious consequence of the substantial dietary changes in Finland.[7,8] The use of saturated fats (mainly milk fat) has decreased by a third from the early 1970s, and the use of vegetable oils has increased. In 1972, 90% of people in eastern Finland used butter on bread compared with 10% in 1992. Vegetable oil was rarely used for cooking 20 years ago whereas 30% of people now use it regularly. Most people have changed from fatty milk to low fat or skimmed milk. The annual consumption of vegetables has increased from about 20 kg per person to about 50 kg.

The findings of our study show that the population strategy for preventing ischaemic heart disease in Finland has been successful. In 1972 the North Karelia project was established as a national pilot programme to lower the world's highest known coronary mortality by lowering the important risk factors.[9]

### CHANGES IN RISK FACTORS ARE LIKELY TO EXPLAIN DECLINE IN MORTALITY

The changes in risk factors seen in our study seem to have explained almost all of the change in mortality in the 1970s. The difference between the observed and predicted mortality, with the 95% confidence intervals taken into account, suggests that in the 1980s the decline in mortality was faster than that predicted by the observed changes in risk factors. The improvement in treatment of acute myocardial infarction may be one explanation: thrombolytic treatment, coronary bypass surgery, and the prophylactic use of aspirin were introduced on a large scale during the late 1980s. Secondary prevention in the form of counselling on risk factors has also changed. The data from the North Karelian register of myocardial infarctions indicate that during the late 1980s the rate of recurrent myocardial infarction decreased more than the incidence of actue myocardial infarction.

A comparison of trends, as in our analyses, cannot exclude the possibility that the decline in both mortality and risk factors could be caused by some other, unknown factors. Conclusions on cause and effect cannot therefore be drawn solely on the basis of our analyses. The consistency of our results with previous studies, however, lends credit to the hypothesis that an observed decline in risk factors is causally associated with an observed decline in mortality.

The logistic regression function, based on one baseline measurement, may underestimate the predictive power of the risk factors. If so, the changes in risk factors might explain even more of the observed changes in mortality.

### OTHER STUDIES

Data similar to ours have been published only from Iceland,[3] where the predicted 35% decrease in risk was close to the observed decrease in mortality from ishaemic heart disease. Other studies were not based on actual measurement of risk factors in a random population sample but used various kinds of indirect data to estimate trends in risk factors to predict the changes in mortality. Also, national mortality data rather than population specific data were often used.

In New Zealand 38-51% of the observed decrease in mortality from ischaemic heart disease could be accounted for by the calculated changes in serum cholesterol concentration and tobacco consumption from 1968 to 1980.[2] Estimated changes in diet in Japan were compatible with the increase in mortality from ischaemic heart disease from 1956 to 1970.[10] A decrease

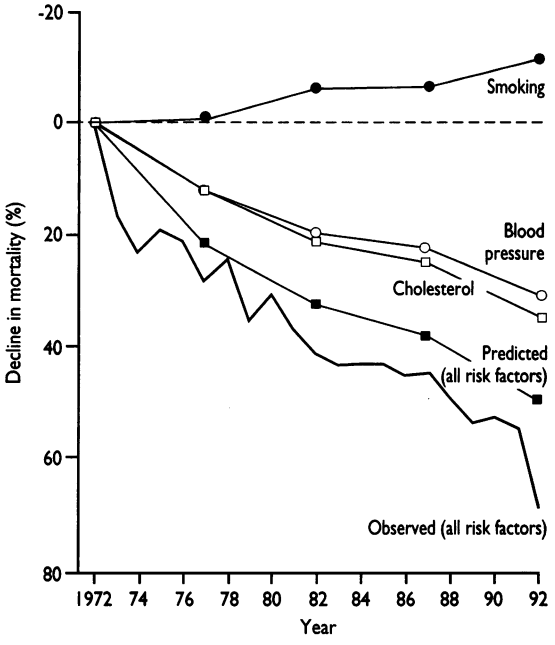


FIG 3—*Observed and predicted decline in mortality from ischaemic heart disease in women aged 35-64 in Finland*

in smoking and better control of hypertension might have also contributed to the decrease in mortality from ischaemic heart disease between 1968 and 1978 in Japan. In Australia the decrease in mortality is compatible with the improved nutrition and reduced tobacco consumption.[11]

Reports from Italy are conflicting: one study showed that mortality from ischaemic heart disease started to decrease around 1978 but that the changes in risk factors had probably not been favourable before that.[12] Another study showed that a multivariate model that included the main risk factors suggested a 10·5% decrease in estimated coronary risk.[13] A comparative ecological analysis of mortality from coronary heart disease in Australia, the United States, and England and Wales found a correlation between trends in risk factors and trends in coronary mortality.[14] In China the increase in mortality from ischaemic heart disease seems to be associated with increases in cholesterol concentration and blood pressure.[15] The results of a comparison of different age cohorts in the Framingham study were used to suggest that the improvement in the profile of cardiovascular risk factors may have contributed to a 60% decrease in mortality from cardiovascular disease.[16]

### UNCERTAINTIES OF STUDY

The main methodological problem with the mortality statistics was how to fix the baseline for the calculations of trend as the annual variation in coronary mortality was large in the early 1970s. We took the mean from 1969 to 1972 to achieve a sufficiently stable baseline estimate; 1969 was also the first year that ICD-8 was used.

A second uncertainty with the trend estimates was how well we could measure the changes in risk factors from 1972 to 1992. The comparability of the results on smoking between our surveys was good. Smoking was assessed with the same questions in all of our surveys. Self reporting of smoking probably did not change much during the years of the study. The change from a short cuff (23 cm) for measuring blood pressure in 1972 and 1977 to a longer one (42 cm) in 1982, 1987, and 1992 may have led to an overestimate of the decrease in blood pressure. The Liebermann-Burchard method used in 1972 and 1977 for determining serum total cholesterol concentration gave values that were 2·4% higher than those given by the enzymatic method used in subsequent years. Although we adjusted for this bias when we calculated the decrease in cholesterol concentration, the real changes in risk factors might have been slightly smaller than those we observed.

The predicted mortalities in our analyses were calculated from the measured levels of risk factors on the assumption that there was no lag time. Results from cholesterol lowering trials suggest that the beneficial effects on mortality from cholesterol lowering are seen as early as two years after treatment.[17] The use of results from the trials at a population level may be misleading because in a population the level of risk factors changes gradually while in trials it falls immediately at the beginning of the trial. The best way to estimate the lag time at a population level would be to measure the level of risk factors as they increase and as they start to decline; data measured in this way, however, are not available. The observed and predicted mortalities in our study have almost parallel declining trends. Assuming a lag time would not change these results very much.

Accurate analysis depends on the power of the chosen logistic regression model. To choose the variables several models were tested. The classic risk factors were included in the model because these are the risk factors that North Karelia and the whole of Finland have aimed to reduce. Socioeconomic factors, measured as years of education, did not affect the coefficients of the classic risk factors. Thus the predicted power of the model was about the same regardless of whether socioeconomic factors were included. Obesity was also tested in the model, but it did not have an independent role in predicting mortality from ischaemic heart disease and was therefore left out. Body mass index in Finland has increased during the past 20 years.[8] Thus obesity does not explain either the change in the levels of the risk factors or the observed decline in mortality from ischaemic heart disease.

In our study the mean age of 55 was included in the logistic regression function. Different ages gave slightly different estimates—for example, the ages of 45, 55, and 60 gave a decline in the predicted mortality of 40%, 43%, and 41% respectively. With the true individual values for age and other risk factors as obtained in the five risk factor surveys in the logistic regression function, the predicted decline in mortality between 1972 and 1992 was 39%. Thus the technical aspects of fitting the model had no meaningful effect on the magnitude of the estimate of trend.

To estimate the role of statistical error in the predicted mortality we calculated the 95% confidence interval. Two types of statistical uncertainties may affect the calculations of a decline in predicted mortality. The first is the sampling error of the mean levels of the risk factors. As the sample sizes were large these errors were small. The 95% confidence interval was largest in 1992, for smoking (SE 2·9), because that year's sample size was the smallest. For blood pressure and cholesterol concentration the sampling error was similar to or smaller than the error of accuracy of measurement. Important statistical error comes from the standard error or the coefficients of the risk factors in the logistic regression model. These errors were smaller among men than women because more men died of ischaemic heart disease. We took both of these errors into account when calculating the confidence intervals. An alternative way to assess the stability of the predicted decline in mortality from ischaemic heart disease is to take the logistic regression from different cohorts. In eastern Finland three different cohorts are available: the present cohort, based on the 1972 survey; the second cohort, based on the 1977 survey; and the third one, based on the 1982 survey. Taking the logistic regression model from different cohorts, changing the follow up time, or pooling the cohorts did not have any significant effect on the predicted decline in mortality from ischaemic heart disease. We took the

### Clinical implications

- A main aim in health policy in Finland has been to prevent cardiovascular diseases by reducing the population level of the classic risk factors
- Our study in two provinces of Finland showed that mortality from ischaemic heart disease declined between 1972 and 1992 by 55% in men and 68% in women
- The predicted decline, based on the changes in risk factors during the 20 years, was 43% for men and 49% for women
- The changes in risk factors explained almost all of the decline in mortality from ischaemic heart disease in the 1970s, but in the late 1980s the mortality declined more than predicted by the changes in risk factors

1972 cohort because the follow up of the observed mortality began that year.

NORTH KARELIA AND KUOPIO REPRESENT FINLAND

The levels of risk factors decreased more in North Karelia than in Kuopio during the first five years, but after that the trends were similar.[18] The trends in mortality in the 1970s and early 1980s have been published.[18-20] The differences between the provinces have been small compared with the overall decline. To bring more stability to the analyses we pooled the data for the two provinces. In the whole of Finland the decrease in mortality from ischaemic heart disease was about 50% from 1970 to 1992. Finland is a small country with a homogeneous population, and the socioeconomic variation in the country is small; North Karelia and Kuopio probably represent the development in the whole country. The MONICA project[5] will give better possibilities to assess the role of changing risk factors in trends in incidence of, and mortality from, coronary heart disease not only in Finland but also worldwide.


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# Community survey of long term daytime use of benzodiazepines


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*See editorial by Tiller*

Media coverage suggests that many people are addicted to benzodiazepines and keen to stop taking them. Our recent efforts to recruit subjects into a programme offering withdrawal, however, had a disappointing response. As a result we initiated this survey. Our decision to study patients taking benzodiazepines long term reflects the current medical opinion that long term use is likely to cause problems.[1]

## Patients, methods, and results

Subjects were recruited from a general practice serving 13 000 patients. The catchment was mixed, including prosperous suburbs and council estates. Using the practice's computerised records for repeat prescriptions we identified all patients taking benzodiazepines during the day and included those in the survey who had been prescribed the drugs for more than one year. Patients were interviewed at home. Psychiatric history and detailed histories of benzodiazepine use were taken. Patients completed the benzodiazepine withdrawal symptom questionnaire.[2] Data were analysed using $\chi^2$ and two sample $t$ tests.

Sixty five patients had been prescribed benzodiazepines for more than one year (point prevalence 0·5%). Eight refused to be interviewed and two were not contactable. Fifty five were therefore interviewed (14 men, 41 women; mean age 57·4 years). Demographic details of those not interviewed were not significantly different from those of the study cohort.

The only variable differentiating between patients keen to stop their treatment and the rest of the cohort was age: those desiring to stop were younger (53·8 years *v* 61·4 years (95% confidence interval of the difference 1·4 to 13·8 years), P=0·037). Patients who had suffered withdrawal symptoms (physical dependence) as measured by the questionnaire were less likely to think that they still benefited from the benzodiazepine (11/17 *v* 32/35, $\chi^2$=5·72, P<0·02). They were younger than those with no history of physical dependence (50·9 years *v* 60·3 years (1·8 to

*Patterns of use, attitudes towards use, and problems with dependence among patients taking benzodiazepines long term during day*

| | No of patients (n=55) |
|---|---|
| Pattern of use: | |
| Daily dose (mg equivalents of diazepam): | |
| >30 | 5 |
| 10-30 | 20 |
| <10 | 30 |
| Dose increased* | 3 |
| Benzodiazepine underused* | 14 |
| Dose varies daily* | 38 |
| Treatment continuous for >5 years* | 42 |
| Previous episode of long term use* | 24 |
| Attitude towards use: | |
| Treatment beneficial* | |
| Currently | 44 |
| Previously | 52 |
| Want to stop taking* | 28 |
| History of withdrawal symptoms on questionnaire† | 17 |
| Psychiatric history: | |
| None | 15 |
| Inpatient | 15 |
| Outpatient | 34 |
| Contact with community psychiatric nurse | 27 |
| Current drug treatment: | |
| Antidepressant | 16 |
| Neuroleptic | 3 |
| Non-psychotropic | 43 |

*One patient omitted owing to mental handicap.
†Three patients unable to complete questionnaire owing to dementia, stroke, or mental handicap.