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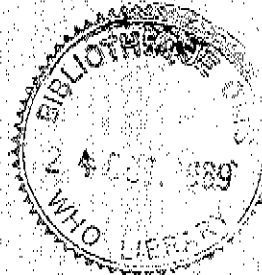


ORGANISATION MONDIALE DE LA SANTÉ
BUREAU RÉGIONAL DE L'EUROPE

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ЕВРОПЕЙСКОЕ РЕГИОНАЛЬНОЕ БЮРО

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ASSESSMENT OF THE RELATIONSHIP BETWEEN COMMON RISK FACTORS AND MORTALITY

Report on a WHO Meeting

Heidelberg
12-14 April 1989

1989

EUR/HFA target 35

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TARGET 35

Health information systems

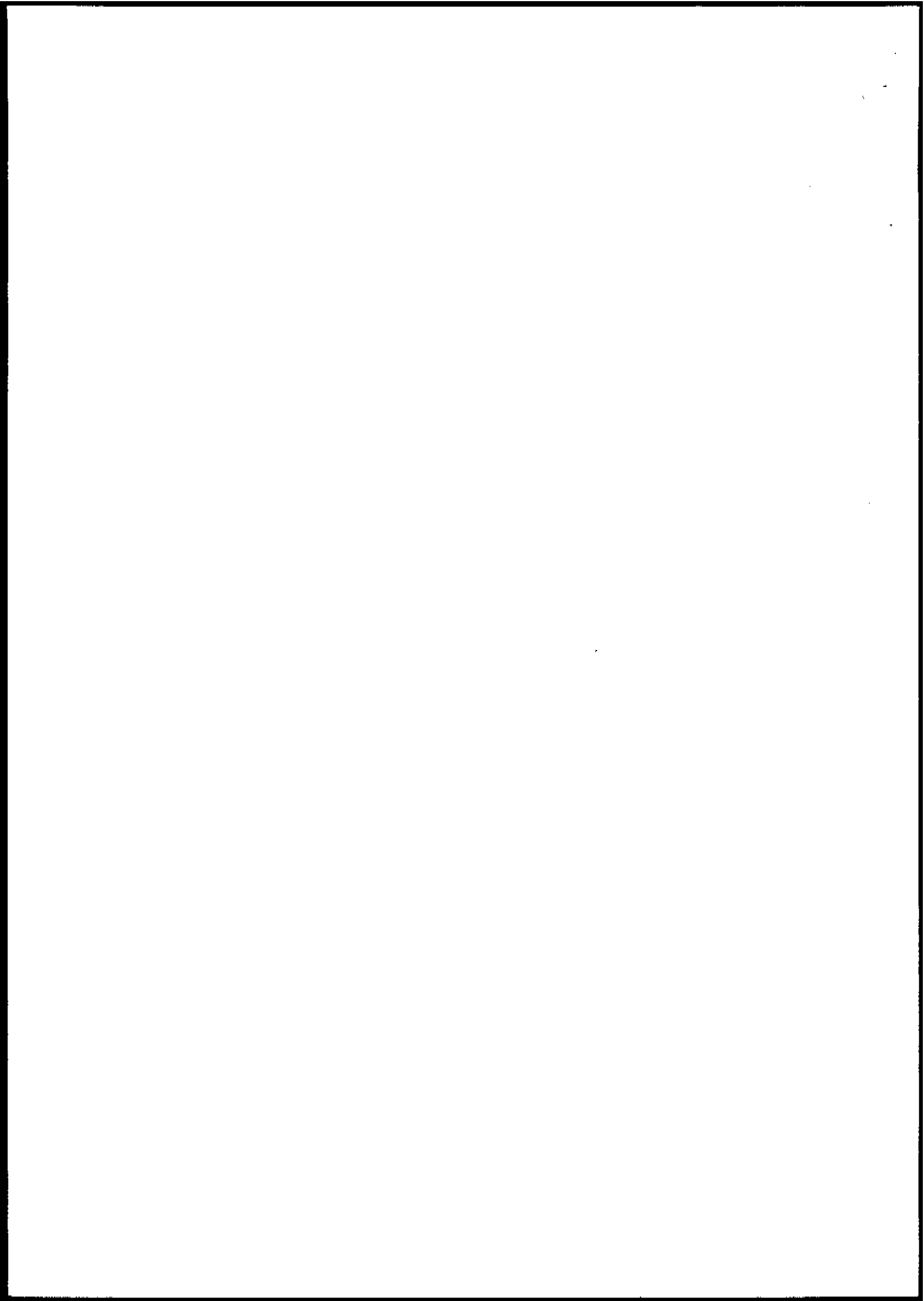
Before 1990, Member States should have health information systems capable of supporting their national strategies for health for all.

Index:

RISK FACTORS
EVALUATION
MORTALITY
MORBIDITY
EPIDEMIOLOGIC METHODS

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1. Introduction

The meeting was opened by Professor E. Nüssel who pointed out the scientific and practical importance of the new project which is being developed by the WHO Regional Office for Europe. He expressed his satisfaction that this meeting is being held in Heidelberg where a large data base was established for the ERICA project and which could serve now for new scientific developments. Wishing the meeting success he expressed his hope that this new project being developed by such an interdisciplinary group of experts will reciprocally assist the ERICA project by providing innovative ideas and methods for further data analysis.

Professor G. Schettler, President, Heidelberg Academy of Sciences, welcomed the participants of the meeting. Nine participants from Czechoslovakia, the Federal Republic of Germany, Finland, Italy and the USSR attended the meeting. At the Academy, where research into epidemiology, pathogenesis and prevention of various diseases has a long lasting tradition. He stressed once again the importance of tackling the problem of chronic diseases through a multidisciplinary and integrated approach.

Dr R. Prokhorskas welcomed the participants of the meeting on behalf of the Regional Director, Dr J.E. Asvall. Introducing the scope and purpose of this meeting he has formulated them as follows:

1. to discuss the general philosophy and organizational framework of the proposed project;
2. to discuss the results of the preliminary analysis performed on prospective data from several epidemiological studies that have been made available at this stage;
3. to identify existing methodological problems and to discuss methods for the integration of epidemiological data from different studies and construction of generalized risk functions for selected risk factors;
4. to discuss the possibilities and approaches to develop comprehensive models linking epidemiological and demographic phenomena, i.e. risk factor distributions and mortality levels in the population;
5. to identify possible areas of practical application of the project results.

Dr A. Menotti was then elected as Chairman of the meeting and Dr V. Grabauskas as Rapporteur.

2. Background

Advances in population studies have led to the formulation and adoption by WHO and its Member States of the strategies for the prevention of cardiovascular and other noncommunicable diseases (WHO Technical Report Series No. 678). Scientific evidence for the population strategy, high risk strategy and secondary prevention in already sick people came from numerous epidemiological studies which demonstrated the existence of the relationship between the risk factors and diseases concerned. However, in practice dialogue still continues on how far one can go both with the population and high risk strategies in the implementation of a large scale of public health programmes which are based on the postulate that modification of risk factors should lead to the decrease of the disease in the population.

Together with other problems that exist, one of the important issues here is that still good models to assess the risks of the disease and to project its outcome are not developed. This is to a great extent related to the uncertainty in risk factor relationships with the disease occurrence (both morbidity and mortality) because the findings from various individual epidemiological studies are inconsistent and sometimes even conflicting. One of the possible explanations for this might be that usually these studies are too small to describe the association between risk factors and morbidity or mortality sufficiently in detail and with a high level of significance with due evidence that estimated associations are valid also in other populations. Consequently, although the amount of individually collected information is really huge, its use in public health practice is very limited. The integration of existing data from various studies by means of pooling, unified analysis and refinement may considerably increase the comprehensiveness and significance of epidemiological findings, providing enough data for the fuller description or risk functions for selected risk factors when linking them up to the occurrence for major noncommunicable diseases and mortality caused by them. The meta-analysis of published data is not able to solve this problem because the data from single studies are analysed and their results are usually published in a non-comparable or too aggregated form.

The need to have a more precisely described risk function is also coming from another conceptual expectation that the majority of biological risk factors may have an optimal level, corresponding to the minimal risk for individual and that the risk can increase if the risk factor level deviates in any direction from the optimal level. Extreme low levels of risk factors like the high ones may be equally incompatible with life. This means that the risk function is not linear (U- or J-shaped) and in this case a substantial amount of data is absolutely necessary for the correct assessment of the risk function. Nevertheless, until recently the data analysis in the majority of epidemiological studies was done making an assumption of linearity or log-linearity of the risk relationship for which a smaller data base was and could be used.

Using the opportunity that the WHO Collaborating Centre for Research and Training in Cardiovascular Diseases at the Institute of Clinical Social Medicine in Heidelberg has established a large data base for the ERICA (European Risk and Incidence, a Collaborative Study) project, WHO has proposed that in collaboration with the above Centre, as well as the other interested European research centres, the appropriate project on the assessment of the relationship between common risk factors and mortality is launched. The first steps in the integrated analysis relating conventional cardiovascular risk factors to total mortality in the follow-up have already been done by the Rome group on Seven Countries Study Data and the Kaunas group on Kaunas-Rotterdam Intervention Study data which present a considerable interest. It is expected that the integration into this project of data from as many as possible European studies will, in general, help to make existing epidemiological data on common risk factors and the risk of major noncommunicable diseases better known and, through the development of generalized risk functions, wider used in practice.

3. Aims and objectives of the project

1. Research goal

The principal goal of the project is to develop a set of generalized risk functions relating selected risk factors to total mortality which would be constructed on the basis of analysis of pooled data from a number of epidemiological studies.

2. Operational goal

To develop reliable risk assessment methods for health planning purposes with a view of facilitating the modelling of expected trends of mortality if levels of selected risk factors in the population are to be modified.

3. Objectives

1. To facilitate the access to, and use of, existing epidemiological knowledge on the contribution of the widely recognized cardiovascular risk factors to major noncommunicable disease and total mortality by means of integration of data and findings from single epidemiological studies.
2. To search for additional data as appropriate for the tasks of analysis which are not existing in the present ERICA project data base.
3. To develop mathematical and computing methods for the integration of data from different studies including the adjustment procedures for possible confounding variables.
4. To analyse and assess the type of relationship of selected risk factors and mortality as well as the variability of risk functions among single studies and to construct generalized risk functions where appropriate.
5. To develop models on the basis of generalized risk functions for modelling the relationships between distribution and level of selected risk factors and mortality in the population. The simulation of intervention scenarios would be the main application of such models.

4. Organizational policy

Due to the efforts of the ERICA project group and its management centre in Heidelberg a remarkable data base has been established. The participants of the meeting felt it worthwhile to use part of these data for the purposes of a new project. To avoid unnecessary duplication and overlapping of the efforts in data analysis, the recommendation was made for this project to concentrate on new methods and models of the risk assessment of total mortality, since ERICA, as originally designed, will cover coronary heart disease mortality and total mortality, using the logistic regression method. While ERICA is confined to studies from the seventies, the new project will also include more recent studies. An appropriate request from the WHO Regional Office for Europe to the ERICA Coordinating Group was felt necessary to reach formal agreement for the use of some ERICA data. The requests to individual ERICA centres for additional information to be collected for the purposes of a new project should be sent from WHO. In case it is related to the data processing procedures at the Heidelberg Centre it should of course be coordinated with this centre. Another possibility for entering new information to the pool for the purposes of this project might be the provision of aggregated data analyses in an agreed scheme and using the same methods. However, preference should be given to the pooling on the individual data level.

5. Variables in the model

It goes without saying that other factors in addition to conventional cardiovascular risk factors are also important or might even be more important for the risk assessment of total mortality. Furthermore, the suggested list of risk factors to be related to total mortality at this stage of the project is also restricted for a simple reason that:

1. these risk factors are definitely measured by many epidemiological studies and are available in the ERICA data base;
2. there is a high probability of having them measured in different studies in a standardized way, therefore one can expect they are comparable enough.

This is why with all the limitations, the suggested list of selected risk factors to be used for the joint analysis at the initial stage of the project is as follows:

- blood pressure (systolic and diastolic)
- cholesterol
- body mass index
- smoking.

All-cause mortality was suggested to be used as an end-point to relate it to the above-risk factors. Cancer mortality should be the next on the list followed possibly by cardiovascular mortality.

2) The assumption of proportional hazards assuming that the contribution of certain risk factor to the risk of death has rather multiplicative than additive nature, i.e. by changing the level of factor the risk is being changed proportionally to the certain baseline risk level. As the result of this assumption the relative risk instead of absolute risk may be used for analysis and generalization. The use of relative risk allows to reduce the influence of possible incompleteness of follow-up data or other factors causing the absolute number of deaths in each study.

3) The assumption that the relationship between all-cause death risk and the level of blood pressure, cholesterol, body mass index and perhaps some other biological factors should be u-shaped. This assumption is supported by the results of many epidemiological studies.

8. General outline of analysis and some illustrative results

Participants in principle agreed with the proposed method of analysis for the estimation of generalized relative risk function (Annex 2). It was accepted as a simple univariate approach which could be used at the first instance. The use of relative risk reduces bias due to possible incomplete follow-up data and allows to include in the analysis studies with different follow-up periods (assuming that cumulative risks have approximately the same linear nature, at least for the period 5-10 years of follow-up).

A rough analysis has been performed on some presently available data to get the first impression on the reasonability of the project goals and the applicability of the proposed analysis scheme to integrate prospective data from different studies. Two pools of data were analysed separately. The data contained measurements of risk factors under consideration for males aged 40-60 at the baseline examination and information about death cases during a certain follow-up period. POOL 1 includes data from two studies in Kaunas and one in Rotterdam. POOL 2 includes 12 studies from ERICA data base having follow-up data. There were individual data for 11 499 males in POOL 1 with 1 159 death cases during the average follow-up of 8.4 years. The corresponding figures for POOL 2 are 23 488, 1 490 and 8.0. Before calculating the relative risk, age-adjustment of blood pressure, cholesterol and body mass index was made using linear regression model. Having calculated the relative risk at different levels of risk factors for each single study, the SAS procedure RSREG was applied to estimate the parameters of quadratic approximation. To visualize the fitness between approximated and observed risks, the weighted average of observed relative risks were calculated and plotted together with approximation (see Annex 3). It can be seen that the quadratic approximation of the relative risk relationship to the analysed risk factors is acceptable in most cases.

Issues to be taken into account when analysing data were also discussed. It was felt that the analysis of the variability of risk functions among individual centres is essential. The influence of the age and the length of follow-up period on the parameters of risk function should also be investigated. Needless to say that for such a type of analysis much more data are needed.

The list of additional information which would be desirable to collect for further data analysis included:

- smoking duration
- alcohol consumption
- diet
- blood sugar
- physical activity
- respiratory function
- marital status
- educational level.

6. Eligibility suggestions

Two aspects of eligibility to join the project have been discussed:

1. general requirements for the centre
2. quality of the data.

The most important general requirements are:

- (a) the study sample should represent the general population, not a hospital one;
- (b) the measurements should be made, keeping widely accepted criteria for standardization procedures (special training of the team, quality control for laboratory measurements, etc.);
- (c) careful registration of death cases in the originally examined sample;
- (d) sufficient length of a prospective follow-up.

The quality of the data provided by each centre should be carefully checked. The biological variation of the variables concerned would be welcomed for the purposes of the construction of risk functions. However, the appropriate methods should be applied to scrutinize the data base and identify those outliers which are far from biological variation.

It was suggested that a simple table reflecting cause-specific contribution to the structure of mortality in each individual centre was necessary to construct and assess it before going into all-cause mortality issues. This will help to identify data with insufficient registration of death cases during the follow-up.

7. Underlying assumptions for constructing generalized risk functions

1) The assumption that underlying biological mechanisms which are causing interactions between blood pressure, cholesterol, body weight, smoking or other factors and the risk of diseases or death are similar in any population. Variations which are being observed among the results of the prospective studies may apparently be explained by the insufficient sample size, differences in methodologies applied or by usually unknown confounding factors.

9. Applicability of results and their final presentation

The practical application of the model or set of models under development might cover at least three broad areas:

1. research projects
2. health programme planning to shape interventions
3. individual risk assessment development techniques for educational purposes.

The use of developed models for research purposes will definitely depend on the interests and tasks of these projects. Therefore, there is no need to have a strictly defined way of result presentation. However, since a major final product of the project is development of relatively simple and user-friendly technique to be used by health planners for public purposes, the format of presentation of the results should be easily understandable.

One of the ways of result presentation might be e.g. analysis of excess mortality compared to a reference level. This reference might be a local baseline situation, average situation as assessed from the data by participating centres in the project, European standard, best desirable etc. The content of this final product might be presented in manuals, tables, graphs, computer programmes, etc.

Although the models constructed are clearly devoted to the population risk assessment, attempts to develop the instruments for individual risk assessment have been felt desirable to be used as a vehicle for educational purposes in individual patient counselling and health intervention programmes.

10. Proposals for managerial structure

Depending on the final decision by WHO, the following managerial structure to facilitate the project development and realization was suggested by the participants of the meeting. It was felt helpful to have a research group chaired by WHO staff member. The membership of this group was suggested, based on the experience that would be needed for further progress of the projects. The tentative list of nominees included:

- Dr R. Prokhorskas, project leader;
- Professor E. Nüssel, representing ERICA project and Heidelberg centre;
- Mr W. Morgenstern, representing statistical science, CINDI and Heidelberg centre as holder of ERICA data base;
- Professor A. Menotti, representing expertise in risk assessment for multiple disease outcomes;
- Dr M. Hakama, representing cancer epidemiology expertise;
- Dr V. Grahauskas, representing expertise in Integrated Programmes for Community Health in Noncommunicable Diseases;
- representatives of WHO headquarters and MONICA project were felt necessary to be identified.

11. Main conclusions and recommendations

1. There is a definite need for better use of existing epidemiological data for the risk assessment in relation to total and cause-specific mortality and finding ways of closing the gap between the existing epidemiological knowledge and its utilization. This may be facilitated by providing the health planners with relatively simple and reliable methods for the projection of health status of their populations.
2. An agreement was reached that it is worthwhile to elaborate generalized Model Risk Functions for Europe relating selected risk factors to total mortality, based on data from a number of epidemiological studies. Depending on data availability and for the pragmatic purposes, mortality end-points rather than pathogenetic ones should be taken into account at the first instance.
3. The principal task for the project would be the population risk assessment. However, with all limitations the attempt might be made at a later stage to assess individual risks which could be used as a powerful educational vehicle to motivate people to change their life-styles.
4. In view of the limited number, both in terms of individuals examined and end-points accumulated in single epidemiological studies, the need for the pooling of the data is obvious. However, it meets with a number of methodological problems. Therefore the criteria for the eligibility for individual centres to join the "pool" should be carefully taken into consideration and the quality of the data checked.
5. The preliminary analysis made with the data from 14 prospective studies has confirmed the expectation that the relationship between selected risk factors (blood pressure, cholesterol, body mass index) and all-cause mortality as assessed by the relative risk function is u-shaped, thus indicating that appropriate methods which recognize the possible form of the relationship should be applied for further data analysis.
6. Although being open for the inclusion into analysis of other risk factors and conditions (e.g. environmental) it was felt necessary to limit the analysis at this stage to a small set of well defined risk factors, namely blood pressure, cholesterol, body mass index and smoking, relating them to total mortality.
7. The further step would be the use of developed risk function in modelling different intervention scenarios to assist health planners and decision-makers in their strategic tasks.
8. A major final product of the project is the development of a relatively simple and user friendly technique to be used by health planners for public health purposes. The format of presentation of the results obtained should be easily understandable. One of the ways of result presentation might be e.g. analysis of excess mortality compared to a reference level. This reference might be a local baseline situation, average situation as assessed by data from participating centres, European standard, best desirable, etc. The content of this final product might be presented in manuals, tables, graphs, computer programmes, etc.

Annex 1

LIST OF PARTICIPANTS

TEMPORARY ADVISERS

- Dr V. Grabauskas (Rapporteur)
Kaunas Medical Institute, Kaunas, Lithuanian SSR, USSR
- Dr Matti Hakama
University of Tampere, Department of Public Health, Tampere, Finland
- Dr S. Mariotti
Istituto Superiore di Sanità, Laboratorio di Epidemiological e
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- Professor A. Menotti (Chairman)
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- Mr W. Morgenstern
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Klinikum der Universität Heidelberg, Abteilung Klinische Sozialmedizin,
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- Dr M. Rusnak
Research Institute of Medical Bionics, Bratislava, Czechoslovakia
- Mr R. Scheidt
Klinikum der Universität Heidelberg, Abteilung Klinische Sozialmedizin,
Heidelberg, Federal Republic of Germany
- Professor J. Wahrendorf
German Cancer Research Centre, Institute of Epidemiology and Biometry,
Heidelberg, Federal Republic of Germany

9. The establishment of the research group to assist WHO in the further development of the project was recommended which should operate under the guidance of the project leader from WHO.

Annex 2

PROPOSALS FOR THE ESTIMATION OF THE RELATIVE RISK FUNCTIONS
 AND GENERAL MODEL OF RISK FACTOR DISTRIBUTION AND MORTALITY

The relationship between the risk factor levels and mortality for a certain population may be expressed in the following way:

$$M(a, a+n, f_1, f_2) = \int_{r=a}^{r=a+n} \int_{f=f_1}^{f=f_2} P(r, f) R(r, a+n-r, f) df dr,$$

where

$M(a, a+n, f_1, f_2)$ - mortality among people having risk factor levels in the range f_1, f_2 at age interval $a, a+n$.

$P(a, f)$ - distribution of population by age and risk factor levels. It may be estimated using data of cross-sectional surveys in given population. This is the place where simulation of different prevention scenarios can be applied, i.e. by modifying the risk factor distribution, moving it to lower levels, cutting off high levels, etc.

$R(r, k, f)$ - risk function for a given population denoting risk of death during age period $r, r+k$ for a person having risk factor level f at age r .

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Epidemiology and Statistical Methodology

Dr E. Shigan
Director, Noncommunicable Diseases

2) Calculate person-years of follow-up, risk and relative risk for each risk factor class in each study

3) Calculate the weighted average of the relative risk in each class, using person-years as weights.

4) Assume that the relative risks for different levels of risk factor and studies are experimental points of certain quadratic process. Apply quadratic regression model using SAS procedure RSREG.

5) Compare approximation (4) and weighted average (3). Both may be used in the model but the parametrical form (approximation) is more convenient and flexible for further calculations.

The relative risk should be estimated for each sex-age group in order to take into account the influence of age on the parameters of relative risk function. If wide age groups have to be used (not enough data), the age-adjustment of risk factor level should be made before starting the above analysis.

The model, as it is presented above, may be used for the simulation of prevention scenarios assuming full risk reversibility. This means that prevention effect as simulated by the model normally should be considered as extremely optimistic, and it may be used as upper limit of feasible prevention effect. Appropriate modifications of the model should be made in order to take into account the reversibility of risk at different ages and time lag between modification of risk factor and its effect on mortality.

The modification of the model, taking into account more than one risk factor simultaneously, should also be considered.

A number of simplifying assumptions have to be made in order to estimate the risk function. Accepting the model of proportional hazards, risk function may be expressed as:

$$R(a, n, f) = M(a) \cdot RR(a, n, f), \text{ where}$$

$M(a)$ - age-specific mortality of given population (national mortality data is widely available).

$$RR(a, n, f) = \frac{R(a, n, f)}{R(a, n)} \quad \text{- ratio of factor-specific risk with overall risk}$$

It can be shown that:

$$\frac{R(a, n, f = i)}{R(a, n)} = \frac{1}{P(a, f = i) + (1 - P(a, f = i)) \left(\frac{R(a, n, f = i)}{R(a, n, f \neq i)} - 1 \right)},$$

where

$$\frac{R(a, n, f = i)}{R(a, n, f \neq i)} \quad \text{is relative risk for risk factor level } i.$$

Assuming that mortality and risk factor distribution are known, the relative risk is only component in the model which remains to be estimated. It is proposed, and this is the key idea of the model, to use certain generalized ("standard") relative risk, assuming that it has to be similar in any population. The generalized relative risk function has to be estimated once, using pooled data from many prospective studies and then may be applied to any population, particularly where no appropriate epidemiological studies were carried out. As soon as additional data is available, more accurate and comprehensive versions of generalized relative risk functions may be developed.

Certain simplifying assumptions have to be accepted, at least at the initial step of model development, due to the limited amount of available data:

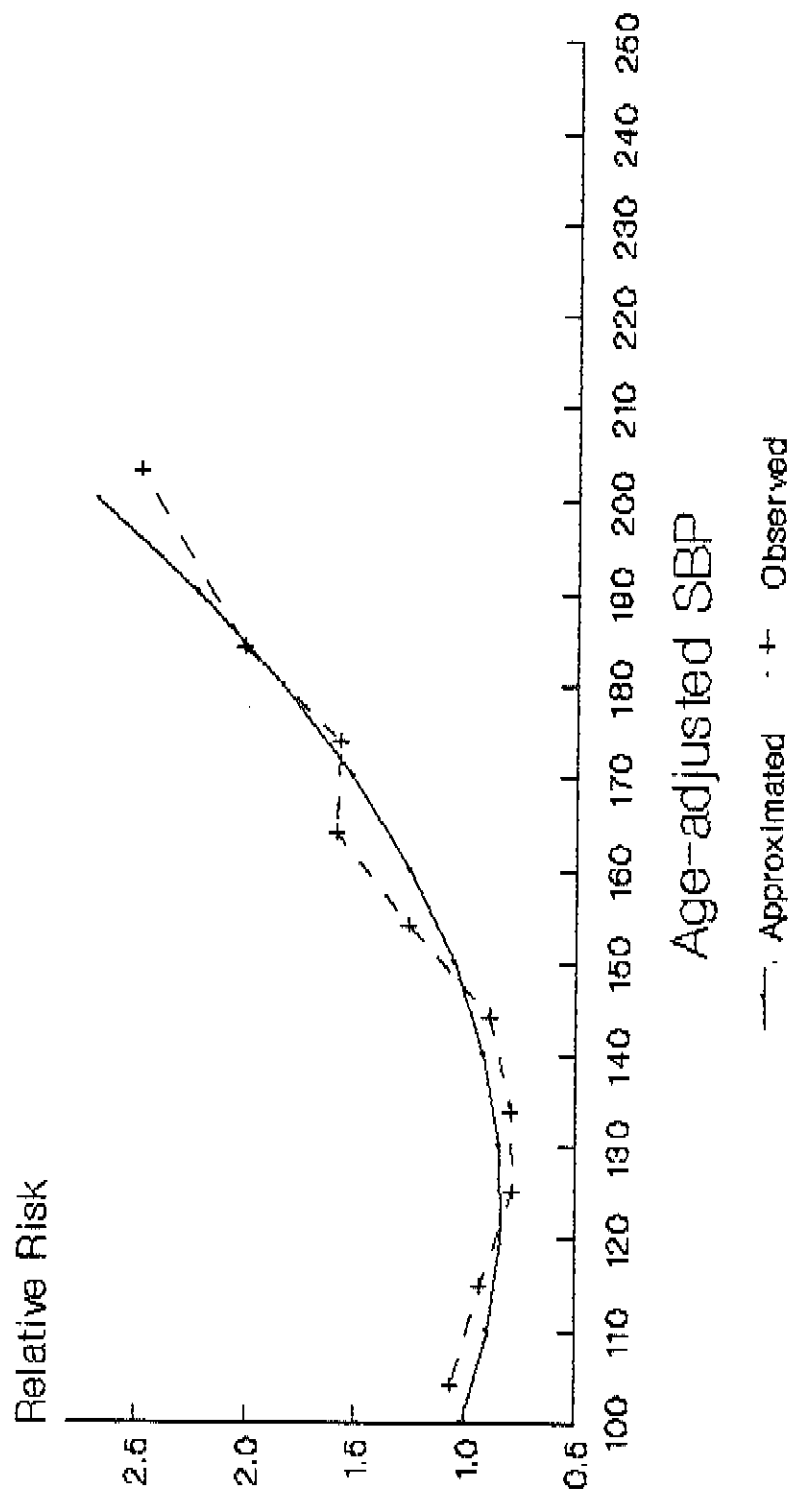
1) The relative risk function is approximately independent from the length of follow-up, at least for 5-10 years. This allows to utilize all available data from studies with different follow-up periods. Of course, one should expect that the predictive power normally should decrease (relative risk function be flattened) along with increasing distance in time between measurement of risk factor and the event (death), which risk is being estimated.

2) The relative risk function relating total mortality and biological continuous risk factors, like blood pressure, cholesterol, or body weight, should be u-shaped. As the most simple approximation, the quadratic equation is proposed to be used at the first instance.

Proposed analysis scheme for constructing a generalized relative risk function:

1) Divide risk factor distribution in each study into 10-15 classes. Deciles may be suitable for this purpose. For smoking and similar factors a common coding should be found.

RELATIVE RISK APPROXIMATION: POOL 1, Age-adjusted Systolic BP & All causes deaths;



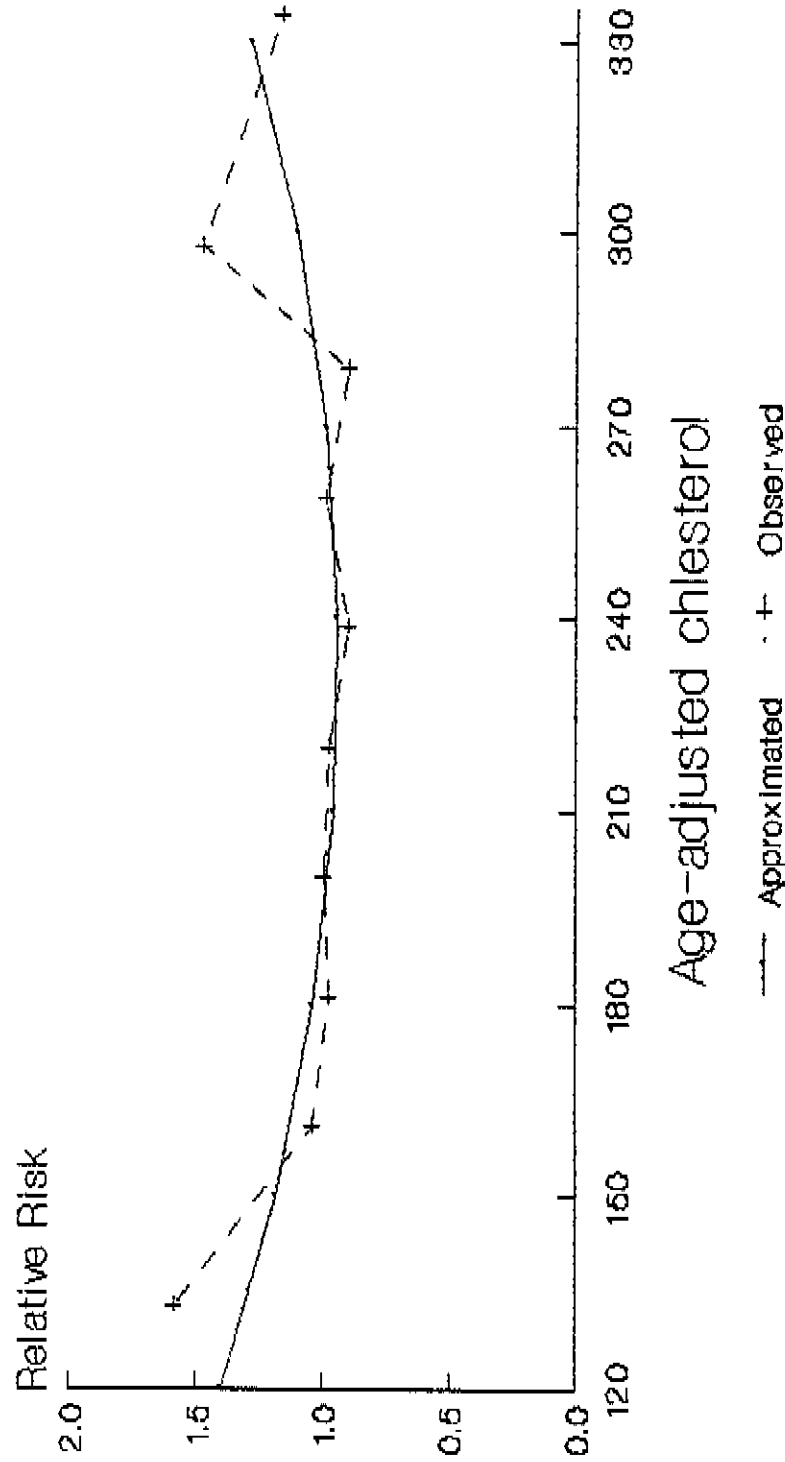
DATA: Kaunas1+Kaunas2+Rotterdam;
N=11499(2455+6679+3365); 1159 deaths(480
+329+350); FU=12.1;7.1;8.8;P.Year=97100;

Annex 3

SOME ILLUSTRATIVE RESULTS

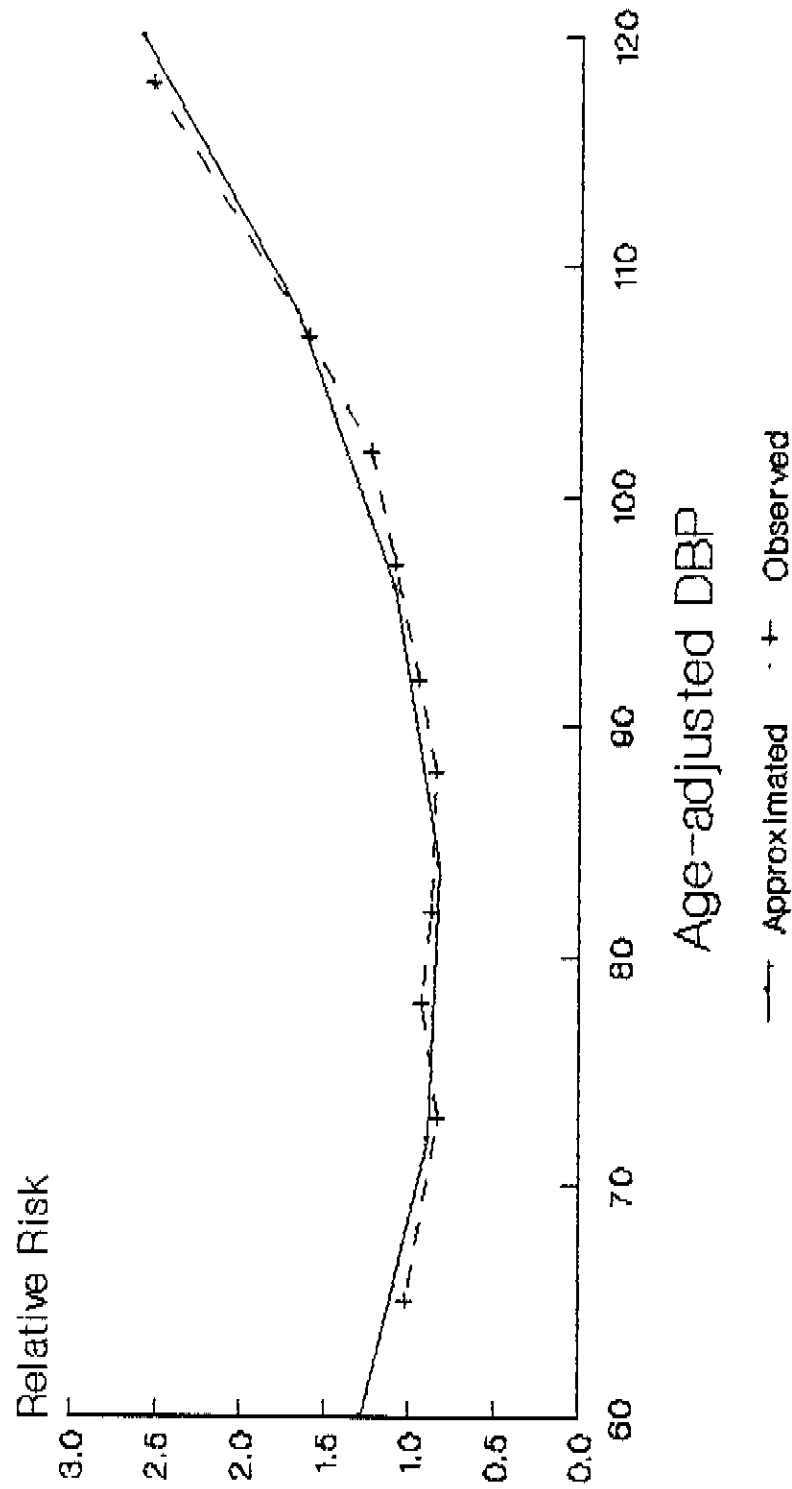
OBSERVED AND APPROXIMATED RELATIVE RISK FUNCTIONS FOR BLOOD
PRESSURE, CHOLESTEROL AND BODY MASS INDEX IN RELATION TO ALL-CAUSES
DEATH RISK (not to be quoted)

RELATIVE RISK APPROXIMATION: Pool 1, Age-adjusted Cholesterol & All causes deaths;



DATA: Kaunas1+Kaunas2+Rotterdam;
N=11499(2456+5679+3365); 1159 deaths(480
+329+350); FU=12.1;7.1;8.8;P.Year=97100;

RELATIVE RISK APPROXIMATION: Pool 1, Age-adjusted Diastolic BP & All causes deaths;



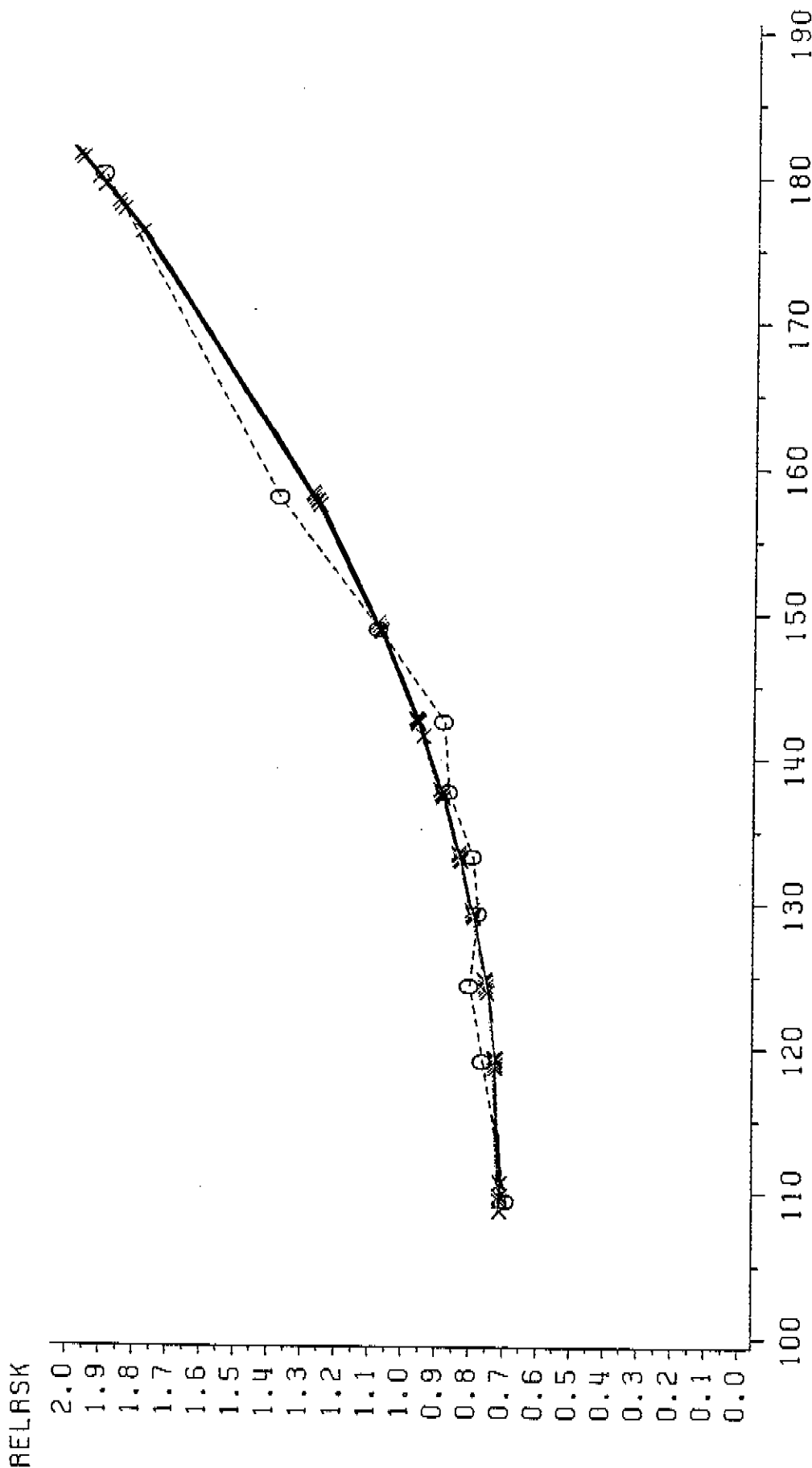
DATA: Kaunas1+Kaunas2+Rotterdam;
N=11499(2455+6679+3365); 1159 deaths(480
+329+350); FU=12.1; 1.8.8.P. Year=97100;

RISK RATIO: AGE--ADJUSTED SBP & TOTAL MORTALITY

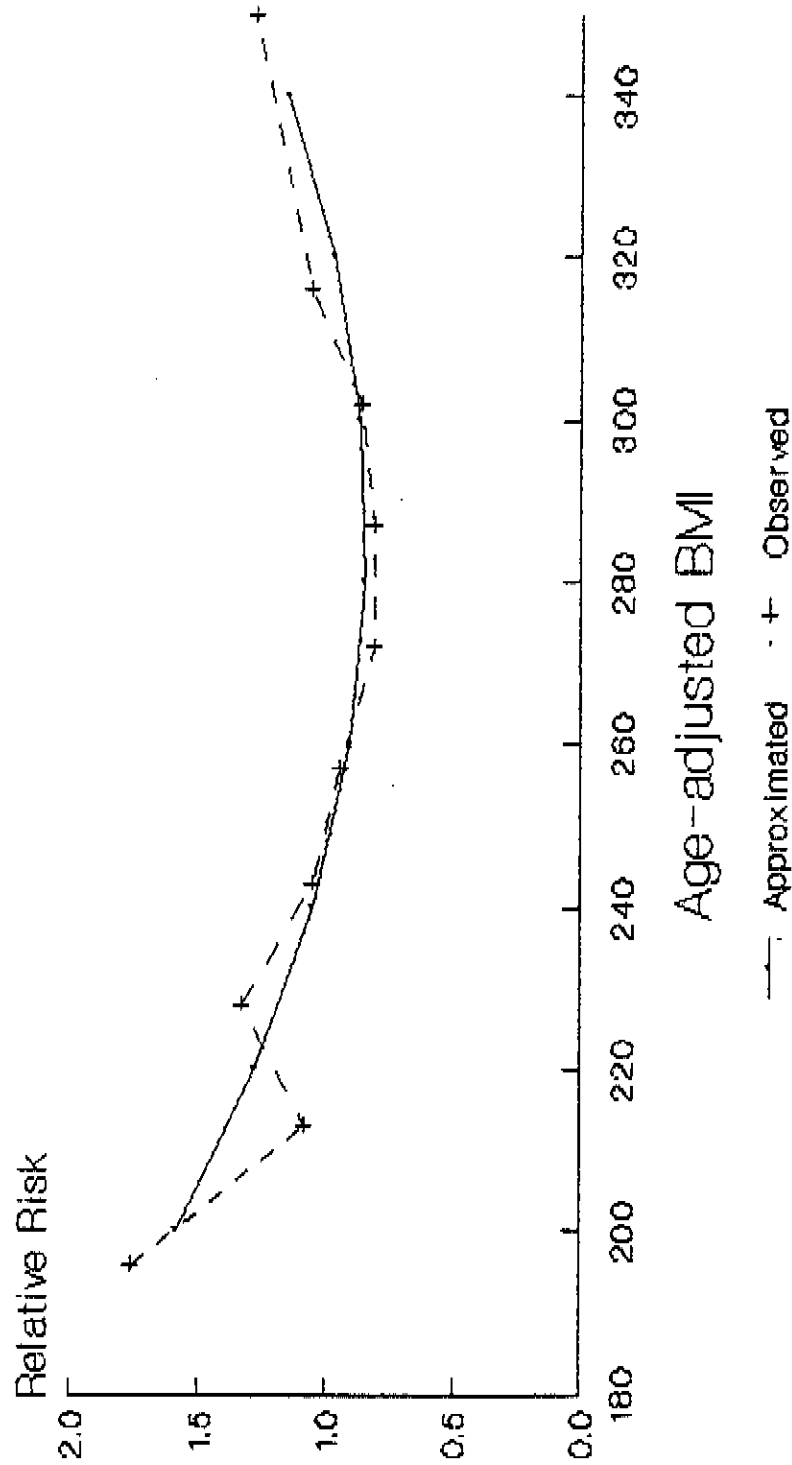
ERICA DATABASE : 12 STUDIES WITH 5-10 YEARS FOLLOW-UP DATA
(MALES AGED 40-60, TOTAL N= APPR.230000)

OBSERVED (O) & APPROXIMATED (X) RELATIVE RISK

Pool 2



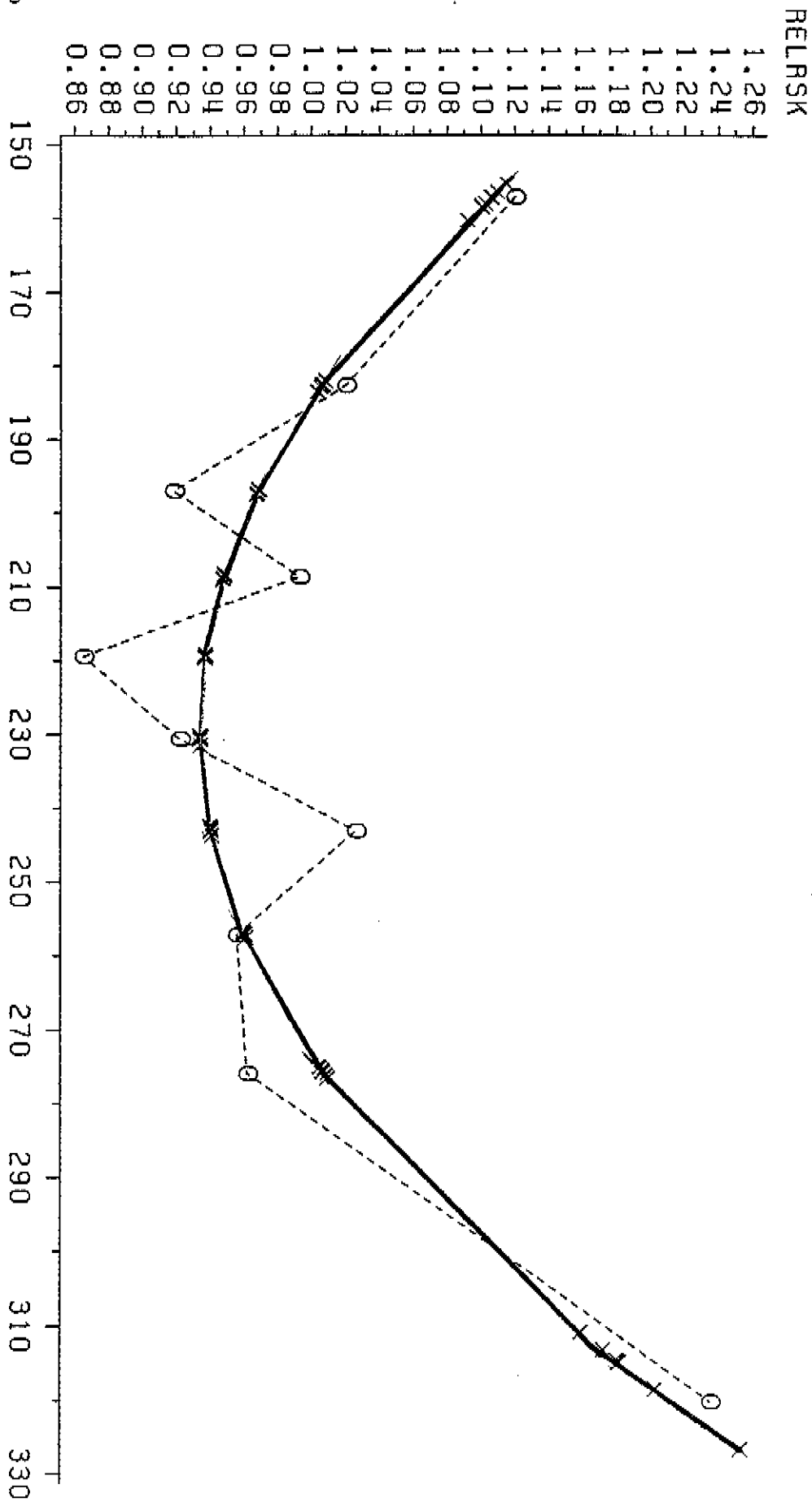
RELATIVE RISK APPROXIMATION: Pool 1, Age-adjusted Body Mass Index & All causes deaths;



DATA: Kaunes1+Kaunes2+Rotterdam;
N=11499(2456+6679+3366); 1159 deaths(480
+329+350); FU=12.1;7.1;8.8;P.Year=97100;

RISK RATIO: AGE-ADJUSTED CHOLESTEROL & TOTAL MORTALITY
 ERICA DATABASE : 12 STUDIES WITH 5-10 YEARS FOLLOW-UP DATA
 (MALES AGED 40-60, TOTAL N= APPR.23000)
 OBSERVED (O) & APPROXIMATED (X) RELATIVE RISK

Pool 2



RISK RATIO: AGE--ADJUSTED BMI & TOTAL MORTALITY

ERICA DATABASE : 12 STUDIES WITH 5-10 YEARS FOLLOW-UP DATA
(MALES AGED 40-60, TOTAL N= APPR.230000)

OBSERVED (O) & APPROXIMATED (X) RELATIVE RISK

Pool 2

