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I. SUMMARY

It is proposed to establish a basic research centre in public health by making use of the unique opportunities for conducting epidemiologic research in Denmark. The centre is a close collaborative network between active research units in combination with a strong central unit. The centre will focus its studies on preventable causes of human diseases such as environmental exposures, life-style factors, and infectious diseases. Advantage will be taken of the remarkable progress within molecular epidemiology which has opened up for better identification of exposures and susceptibility. In combination with a very comprehensive system of health registers, this progress provides new and sharper tools within analytic epidemiology.

The research plan is based upon common approaches to the study of disease etiology, common methods and tools. As part of the work tasks, the centre will also provide advanced research courses and seminars, and will take the lead in the developing of a Ph.D. training programme in epidemiology.

In general, the emphasis of the research plan is on longitudinal studies of long-term health effects of external exposures and genes at different phases of life, ranging from the fetal period to adulthood. The centre will make use of existing registers and of ad hoc collected data in the form of self-reported information or data based upon analyses of collected biological material. The development in biotechnology and in statistical and epidemiological theory and the advancement in computerized data handling should place epidemiology in high priority among the health sciences.

IIa. RESEARCH PLAN: BACKGROUND AND GENERAL ASPECTS

General aim

We propose to establish a Danish Research Centre in Epidemiology for the study of the causes of human diseases. The causes will include environmental exposures (infectious and non-infectious) and individual susceptibility to these exposures, determined by genetic constitution or preceding environmental exposures. Knowledge about the causes of diseases provides the scientific rationale for prevention and treatment of diseases. The centre will be based on interaction between studies addressing specific hypotheses and development of available methodology inspired by the needs and experiences from current studies. Such a centre will be a unique strengthening of the utilization of the excellent opportunities for

epidemiological research in Denmark.

Development of analytical epidemiology

The identification of causes of diseases and quantification of their effects in humans must be based on observations of the association between exposure to putative causes and subsequently increased risk of the disease in human populations, possibly supported by observation of a reduction in risk following intervention against the cause.

During recent years, the methods and techniques for design, conduct and analysis in analytical epidemiology have developed rapidly, and proper application of the methods considerably reduces the risk of biased conclusions. Of particular note is the conceptual refinement and differentiation of epidemiological design options, the technological development in questionnaire and interview techniques, in optical reading of hand-filled forms, in mass analysis of biological samples (for genomic material from humans and infectious microorganisms, immune response components, nutritional biomarkers, toxins, trace elements), in epidemiological statistical theory, and in computational power.

Research opportunities in Denmark

Denmark provides excellent opportunities for epidemiological research for several reasons. The Danish population of 5 million people lives within a small area and exhibits low emigration rate. The society is a developed, stable democracy, which provides public high-standard health services to the entire population. The population is well educated and there is a political as well as a general appreciation of research activities and willingness to help by making personal experience available for research. The structure and function of the society and the health services have for decades implied routine systematic gathering and storing of a wealth of potentially relevant detailed information about the individuals, which is retrievable because it is linked to the individual central person registration number. Using this number, the Central Person Register contains continuously updated information on name, civil and vital status and address.

In addition to this register, the nation-wide general health information systems of particular value for epidemiological research are the following: midwives records; birth register; blood testing of pregnant women and newborns; public health nurse records on infants; school health records; draft board examination records; supplementary pension register (for all employees recording workplace by time); health insurance reimbursement

register; hospital records; pathological diagnosis registers; tissue stored in paraffin blocks; somatic hospital discharge register; central psychiatric register; premature pension registers; death certificate register. A drug prescription register is currently being built up. Furthermore, there is a number of specific disease registers, among which the Danish Cancer Register is the most prominent.

Most of these registers are partly or completely computerized and therefore provide easy and relatively cheap identification of relevant population groups, sampling from these groups, collection of relevant information on the members of the groups through record linkage or direct contact both at baseline and during later follow-up.

Ethical and legal conditions

According to Danish law, all biomedical research projects involving systematic collection of information on human beings must be evaluated on the basis of written research plans and given permission before start by the official regional ethical committee and the governmental data protection office. Data collection involving contact with the individuals requires informed consent. Access to data- or biobanks or to registers, whether primarily established for research or non-research purposes, can be obtained on specified conditions without individual informed consent.

Utilization of the research opportunities in Denmark

As indicated in a recent international evaluation of epidemiology requested by the Danish government, 'the quality and quantity is very good'. However, it is also obvious that much better and greater research production could be achieved. This will require more resources allocated directly to productive and high-quality research groups and a more appropriate organization facilitating research and training.

Analytical epidemiology research has been conducted as an ad hoc activity in institutions both within and outside the Danish universities. Except for the private research institution built up around the Danish Cancer Register (supported by the Danish Cancer Society), there are only fairly small and limited units where analytical epidemiology has priority.

This state of affairs is particularly regrettable in view of the research opportunities. The relative investment in epidemiological research in several other countries, such as the United States, United Kingdom, Holland, Italy, and the other Scandinavian countries, far exceeds

that in Denmark.

On the other hand, there is an emerging appreciation of epidemiology in the research community as well as in the health service system. The Danish Medical Research Council has recently granted two 5-year research professor positions in Epidemiology. New research units have been built or are being planned. New chairs or changes in vacant chairs in related disciplines at the universities are being established.

However, it will be a sub-optimal utilization of these conditions if the possible synergistic effects between related research activities are not stimulated, if overlapping research activities are not coordinated, and if better research organization and training is not developed.

Proposed Danish Research Centre in Epidemiology

We propose to establish a research centre based on a close collaborative network between the existing research units of the proposers combined with a common central unit in one of these research units in Copenhagen. The research plan for specific projects in the centre will have three phases: a) inclusion and continuation of current research activities of each of the participating research units; b) combining these research activities where common specific aims can be identified; and c) development of new common research projects utilizing the expertise, facilities, and resources of the new centre.

The actual data collection may take place in already existing information systems, such as registers and archived biological material (data- and biobanks), or by contact to members of defined human populations. Most research activities in the centre will take place in Denmark, but the occurrence of the disease and its putative causes as well as the need for comparative studies frequently justify investigations in other countries.

Coherence of the research activities of the centre

In addition to the gradual integration and development of research projects, the collaboration in the centre has four dimensions: a) a common basic theory about disease causation and its significance and implications for the study of disease causation and eventually for disease prevention; b) broadness in the scope of diseases and putative causes under study, implying active exploitation of current research opportunities and thereby continuous updating of the knowledge about the health services and the pertinent information systems; c) common methods for design, conduct and analysis, and shared tools, techniques

and facilities; and d) a built-in postgraduate Ph.D. training programme. The integration and development of these dimensions in one centre, where several specific research projects are running, is of obvious benefit, not least to the research projects themselves.

IIb. RESEARCH PLAN: LONGITUDINAL STUDIES OF DISEASE CAUSATION

The research plan puts emphasis on longitudinal studies of disease causation and the long-term effects of specific forms of exposures at different critical phases of life. Many of the hypotheses to be tested require follow-up periods of several decades. Therefore, an important element of the research plan is the already established large population cohorts and the many old and comprehensive population registers available in Denmark. However, the programme will also include data sources from other areas where these can be used to answer particular questions in better ways.

The programme is divided into three main areas according to topic and age at exposure. They deal with long-term effects of early exposures, and represents different approaches to the research aim. The first is called *genetic, fetal and childhood origins of disease* and directed towards reproductive failure and hypotheses of early programming. The second area concentrates on long-term consequences of infections later in life, and include community-based studies on common highly contagious infections, cohort studies of retroviral infections and viral-associated cancers. This area is called *determinants of severity of infections and their long-term consequences for children and adults*. The title of area three is *long-term consequences of non-infectious environmental exposures in adulthood*. The subjects covered in this chapter relate to later appearing environmental and occupational risk exposures for major human diseases such as cancer, cardio- and cerebrovascular diseases.

1. GENETIC, FETAL AND CHILDHOOD ORIGINS OF DISEASE

Background: The risk of many of the major chronic diseases of great socioeconomic impact is influenced by the individual genetic constitution, which may determine the susceptibility to specific environmental exposures. There is an increasing body of evidence indicating that exposures in the pre or early postnatal period are crucial for these diseases. Thus, studies from the UK and Norway show a remarkably close correlation between infant mortality in a given region and mortality 50 years later among the adult males born in that region. Fetal growth and early nutrition appear to be related to risk of several adult diseases.

The mechanism behind the associations are not known, but Barker and his group from U.K. have put forward the so-called "programming hypothesis", which to some extent is supported by animal experiments. This hypothesis suggests that early influences in life programme the way we respond to adult risk factors, for example a diet with a high fat intake. Previous studies of the "programming hypothesis" have been limited to routinely collected data on birth weights and placenta weights. Newborns with a low birth weight in spite of normal placenta weights have been at increased risk of a number of diseases later in life.

Toxic exposures, for example alcohol intake during pregnancy, may have long lasting effects which are not detectable at birth. The same may be true for exposure to smoking in pregnancy. Exposure to diethyl stilboestrole is a classical example of a carcinogenic priming in utero, which decades later could lead to vaginal cancer. A growing body of evidence also link infectious agents, viruses in particular, with disease manifestations decades after the initial exposure. Schizophrenia has been suggested associated with intrauterine exposure to influenza, but also rheumatoid diseases, Crohn's disease, ulcerative colitis, and certain cancers (e.g. testicular cancer) may be linked to intrauterine infections or other intrauterine exposures.

a. Influence of genes and family environment on morbidity and mortality

Aims: To assess the genetic and familial environmental contributions to the familial correlations in risk of morbidity and mortality from cardio and cerebrovascular diseases, various cancers, infections, diabetes, and chronic obstructive lung diseases.

Study population: The study is based on the adoption method in which associations in risk between subjects adopted early in life (adoptees) by non-related parents and their biological relatives are assumed to reflect genetic influences. Furthermore, similarities between the adoptees and the members of the adoptive family are assumed to reflect influences of the rearing family environment.

All non-familial adoptions granted in Denmark between 1924 and 1947 are recorded in the Danish Adoption Register (total 14,000 adoptees). The register includes information on the identity of the biological and adoptive parents. The offspring of the biological parents (biological full siblings, maternal and paternal half siblings) and the other children in the adoptive family (biological offspring or other foster children) can be identified by following the parents through the local population registers. The total population of biological and adoptive families will encompass about 100,000 subjects.

Workplan: The population will be followed up regarding death, causes of death, admission to hospitals, and diagnosis of cancer by record linkage with the Central Person Register, the Death Certificate Register, the Somatic Hospital Discharge Register, and the Danish Cancer Register.

Specific hypothesis will be tested based on nested studies including families in which the adoptee has been diagnosed with the specific disease under study (case-families), and a corresponding number (between 1:1 and 1:5 match) of appropriately selected families in which the adoptees, until the time of diagnosis, belong to the population at risk (control-families). The complete family pedigree will be identified for the case- and control-families, and their morbidity and mortality will be compared using the socalled frailty models.

b. Consequences of intrauterine environmental exposures

Aims: To study short- and long-term consequences of intrauterine environmental exposures in a large prospective cohort of newborns.

Study population: A total of 100,000 pregnant women and their offspring will be enrolled over a two-year period in close collaboration with the Danish obstetrical departments. The time of pregnancy is probably the time period with the closest contact to the health care system, which provides excellent opportunities for data collection. As part of the routine registration, a comprehensive set of pregnancy and birth related data is already available through different registers. The quality of these data is high. What is needed is more information on potential risk factors or exposures.

Workplan: Exposure information will be obtained in the study by using structured questionnaires on life-style factors, occupational exposures, diet and illness during or before pregnancy. It is furthermore possible to link data on medical prescriptions in pregnancy to other data files. The latest development within immunology and molecular biology now allows high-quality trace analyses, hormone detections, and DNA-analyses in considerable numbers of small biological samples. In Denmark, we have access to these new techniques, and all blood from screening procedures during pregnancy and immediately after delivery is received in one place; the State Serum Institute. An important component of the project will therefore be to establish a biological bank including frozen blood cells and serum from the participants. Exposure measures can also be obtained using the stored biological materials. Parts of the biological material will be stored on a long-term basis to enable research on later events. The specific studies will be conducted as nested, retrospective case-control studies

leaving most of the biological materials untouched.

The cohort members will be followed up over time by adding data from existing medical registers, which will make it possible to examine whether some of the known prenatal risk factors are associated with later diseases. The size of the cohort allows nested case-control studies of prenatal causes of some childhood cancers, cancer of the testis and other serious diseases. It will also be possible to study teratogenic effects of the more frequently prescribed drugs in pregnancy and to examine associations between for example occupational exposures and reproductive failures.

An immediate use of the biological bank will be to estimate the risk of miscarriage, fetal deaths and malformations caused by infection with parvovirus B19. This infection has been etiologically associated with erythema infectiosum and has been suspected to cause an increased rate of miscarriage and fetal deaths among women infected during pregnancy. This potential hazard may have particular implications for pregnant women working with small children and immunodeficient patients.

c. Longitudinal studies of health implications of deviant growth of height and weight-for-height early in life

Aims: Investigation of the influence on adult risk of morbidity and mortality from major chronic diseases (cardio and cerebrovascular diseases, cancer, non-insulin dependent diabetes, chronic obstructive lung disease) of deviant growth of height and weight-for-height as cumulative indicators of nutritional exposures from fetal life through young adulthood.

Study population: The study takes advantage of population-based cohorts of individuals who have had their weight and height measured at least two times with an interval of a year or more between the measurements. There are several different population samples available which by combination may provide repeated measures of height and weight. The most important are the following: a) a cohort of about 9,000 children born at the State Hospital 1959-61 and measured at birth, 1 and 3 year. b) The annual health examinations of all pupils between ages 6 and 14 years in the schools of the central Copenhagen municipalities since birth year 1930 through 1964, total about 350,000 individuals. c) Mandatory draft board examinations of men aged 18-26 years in the greater Copenhagen area and surroundings since 1943, and in the provinces of Zealand since 1964, total about 400,000 until 1977.

Workplan: The measurements recorded in the existing cohorts will be combined in some studies with length and weight at birth (and gestational age at birth) retrievable from

archives of midwife protocols, and with measurements during infancy retrieved from public health nurse records. Measurements on the parents may be obtained in some subsamples and are relevant in order to control for the well-known genetic influences on both height and weight-for-height. The population samples will be followed up with regard to the occurrence of the major diseases by record linkage with the Central Person Register, the Death Certificate Register, the Somatic Hospital Discharge Register, and the Danish Cancer Register.

The statistical analysis uses methods and models for repeated measurements of continuous variables to describe the extreme levels and deviations in the growth curves for both height and weight-for-height. Individuals with extreme growth curves are compared with individuals with more normal growth curves with regard to their relevance as proxy variables for risk factors with health implications.

2. DETERMINANTS OF SEVERITY OF INFECTIONS AND THEIR LONG-TERM CONSEQUENCES FOR CHILDREN AND ADULTS.

Background: Danish researchers have been involved in community studies of communicable diseases in Guinea-Bissau since 1978. A longitudinal community study design provides the possibility of studies of disease transmission and of assessing long-term consequences of both infections and health interventions.

The longitudinal studies in Guinea-Bissau have provided several unexpected observations. The most important of these are: that transmission factors (intensity of exposure, amplification of severity, cross-sex transmission) were apparantly more important for severity of infection than the host factors (malnutrition, age at infection) which have usually been emphasized; that infections like measles have unrecognized long-term consequences, particularly if acquired early in life; that standard measles immunization reduces mortality with more than expected on the basis of the impact of prevention of measles infection; that mild measles infection may reduce long-term mortality; that the high-titre measles immunization strategy, introduced by WHO, compared with the standard measles vaccine was associated with increased mortality for female recipients. Since these observations contradict long-held assumptions, they raise questions regarding validity, generalizability and mechanism which have to be addressed in the coming years.

Guinea-Bissau is believed to be the epicentre for the HIV-2 epidemic. The two largest HIV-2 infected cohorts in the world are followed in this country by our group. HIV-2, as

other retroviruses, are characterized by slow progression from exposure to disease manifestation. Results obtained so far suggest that HIV-2 is much less pathogenic than HIV-1, and also less infectious. However, much remains to be learned about the nature of HIV-2, including its association with the monkey equivalent, SIV-2. In this respect it is of interest to note that women who prepare and eat monkey in Guinea-Bissau are found significantly more likely to be HIV-2 seropositive than women who do not.

Long-term effects of infection with HIV-1 continue to be an area of great interest, in particular with respect to questions regarding determinants for long-term survival including development of malignancies. The questions will be investigated in well-established homo- and heterosexual cohorts in Denmark, Greenland, and the USA. Further studies of the malignancies potentially associated with the HIV epidemic may give clues to understanding their etiology.

The influence of viral infection on carcinogenesis is an example of a disease process where the time between exposure and disease may be counted in several decades. The often very complex associations between viruses and tumour development may represent not only a direct oncogenic viral potential, but also a more indirect effect through viral impairment of the immune system.

For long, a sexually transmitted agent has been suggested to be involved in cervical cancer for which human papillomavirus (HPV) is a strong candidate. In a recent record linkage analysis, we provided further evidence for a possible association between the etiology of anal and cervical cancer. More recently, we have found strong evidence for an association between immunodeficiency and premalignant anal lesions.

The pattern of occurrence of Kaposi's sarcoma has led to very different opinions on its etiology, one of which is the involvement of an infectious agent, another the involvement of a genetic component. In addition, the clinical manifestation of the disease appears at least partly determined by an individuals immune status.

d. A longitudinal community-based study of determinants and consequences of childhood infections

Aims: The general objectives are to examine the validity and generalizability of some basic principles of infectious disease epidemiology, and to find ways of improving disease control within the framework of primary health care, particularly through immunizations.

Study populations: The current project is following a population of 30,000 people

distributed in three districts in the capital and several rural areas of Guinea-Bissau. Thirty local assistants are involved in routine data collection. Fifteen foreign and local researchers carry out investigations related to the epidemiology and control of infectious diseases.

At home visits with an interval of 1-3 months, pregnancies, births, morbidity, growth, nutritional status, immunizations, hospitalizations and deaths are registered routinely with an interval of 1-3 months for all children under three years of age. Older age groups are examined at least once a year in connection with annual censuses. More intensive data collection and longer follow-up is carried out for twins.

Workplan: Previous studies of measles have documented intensity of exposure, severity of infection of the infecting person, and cross-sex transmission to be the major determinants of fatal infection. The impact of intensity of exposure, dose of infection, and cross-sex transmission will be examined for whooping cough, varicella and polio. Since dose can not be measured directly, it will be measured by length of incubation, which, according to animal models, is a suitable inversely related surrogate for the dose.

We have found both measles and cryptosporidium to be associated with significant excess mortality after the acute phase of infection. Risk factors for delayed excess mortality after infection will be examined for both measles and cryptosporidium as well as severe cases of infection. Long-term mortality will be related to exposure situation, severity of acute disease, immunosuppression during acute infection, vitamin-A depletion, growth faltering and post-acute morbidity.

Mild cases of measles and recipients of low dose measles vaccine have been found to result in unexplained lowering of mortality beyond that gained from protection against mortality attributed to measles. In future studies, it will be investigated whether disease and immunization have beneficial long-term effects on immunological status. It will also be examined whether other infections and vaccines (polio/DTP, whooping cough, BCG) have similar consequences as observed for measles. Should a beneficial effect beyond protection against a specific disease be substantiated in these larger studies, it will be reasonable to examine the impact of immunization and infections in developed countries as well.

e. Longitudinal studies of HIV and related retroviruses in homo- and heterosexual populations

Aims: To study determinants for disease progression and long-term survival among HIV-1 and HIV-2 infected individuals, factors of importance for the development of HIV-

associated malignancies, viral genomic drift through generations of spread, and the association between SIV and HIV-2 specific strains in a community where transspecies transmission (monkey-man) is suspected to take place continuously.

Study populations and workplan: In 1981, a Danish cohort of 259 homo/bisexual men were established to study aspects related to the AIDS epidemic. Within half a year two similar cohorts were initiated in New York City and Washington DC. All three cohorts have been followed up every 1-2 years. A close Danish-American collaboration has ensured that the collection of questionnaire information as well as biological material is harmonized and synchronized, enabling combined analyses. This collaborative effort is planned to continue in the coming years.

Studies of epidemic spread of HIV in a heterosexual context will be based on a project established in Greenland in 1988-89. The programme in Greenland is considered unique for this purpose due to the well-defined and isolated study population, the early initiation and local acceptance of the research programme, and finally the completeness of the registrations taking place. The project includes complete registration of all positive and negative HIV tests performed in Greenland. Case tracing includes the collection of detailed information on sexual exposure, the exact time-intervals for the different contacts as well as other behavioral and demographic variables. Owing to the general features of the research programme, the lack of intravenous drug use, the lack of haemophiliacs, and only sporadic and limited homosexual activity in Greenland, there has not been any problems in defining the modes and directions of the spread of HIV among the Eskimos in Greenland. Based on frozen lymphocytes, viral isolation and characterization will be performed in order to study the potential for viral genomic drift as a consequence of the passage through several generations of humans.

Determinants of HIV-2 infection and its long-term impact on morbidity will continue to be studied based on the well-established community-based cohorts in Guinea-Bissau. Assessment of time-dependent immunological status will also be made using a slide methodology for T-lymphocyte subpopulation determination. Isolates of both HIV-2 and SIV-2 (from monkeys) will be obtained and sequenced to study their degree of genomic association.

f. Studies of cancers with a potential viral etiology

Aims: The immediate objective is to study clues to the etiology of anal cancer, cervical cancer and Kaposi's sarcoma. On a longer perspective, it is the intention to include studies

also on other viral-associated cancers.

Study population and workplan

The following studies of anal and/or cervical cancer are in progress or planned: a) A large case control study of anal cancer. This study is performed in collaboration with Swedish researchers and will include 400 cases and 1000 controls. Questionnaire data and biological materials (blood and tumour biopsies) are collected simultaneously. PCR analyses for human papillomavirus (HPV) and herpes simplex virus (HSV) will be performed together with serological tests for HSV. b) A follow-up of the cohorts of homosexual men in Copenhagen, New York and Washington DC is ongoing in order to study the long-term consequences and interactions of HPV, anal intraepithelial neoplasia and immunosuppression. By combined analyses on the larger sample size, more refined analyses can be performed. c) A cross-sectional study of HIV-positive and HIV-negative women will be finished. The objective here is to study the possible association between cervical and anal squamous cell abnormalities and presence of HPV, the role of immunodeficiency, and finally risk factors for HIV and HPV positivity. d) A merging analysis between the AIDS and cancer registers in the USA will be performed in order to study the relative risk of anal cancer among AIDS patients compared to the general population.

A collaborative record-linkage study of the endemic (non-AIDS) and the AIDS-related Kaposi's sarcoma between Norway, Sweden, Finland, and Denmark is proposed. Only a collaborative effort will supply the necessary number of cases for analytical purposes. Possible time trends in the evolution of endemic Kaposi's sarcoma and identification of groups at increased risk will be assessed, paying particular attention to age and gender distribution, nationality/ethnicity, medical history and marital status. Futhermore, the risk of other primary malignancies among Kaposi's sarcoma patients will be determined. The cancer registers of the Nordic countries will serve as primary resource for identification of cancer cases. Record linkage will be carried out with the Ccentral Person Registers, the AIDS register, the Somatic Hospital Discharge Registers and the Death Certificate Register.

g. Migration study of environmental influences on the development of cancer.

Aims: The cancer incidence distribution, in particular the distribution of viral-associated cancers (cervical cancinoma, nasopharyngeal carcinoma, hepatomas, salivary gland carcinoma) among eskimos in Greenland is very different from that among Danes in Denmark. The aim is to examine, based on these facts, the possible influence of temporary

residence in Greenland on cancer development, in particular cancers hypothesized to be associated with a viral etiology.

Study population and workplan: A cohort of 10,000 Danish migrant workers in Greenland (immigration period 1956-75) is available for the study. Today, the expected number of cancer cases in the cohort is approximately 900. This sample size allows for the detection of even very moderate differences in cancer morbidity. The pattern of incidence of cancer in the cohort will be compared to the patterns expected among permanent residents of Denmark and Greenland of either Danish or Eskimo origin.

3. LONG-TERM CONSEQUENCES OF NON-INFECTIOUS ENVIRONMENTAL EXPOSURES IN ADULTHOOD.

Background: A number of risk factors have been identified for the major chronic diseases and health problems in adulthood, such as various types of cancer, cardio and cerebrovascular diseases, non-insulin dependent diabetes, chronic obstructive lung disease, and subfecundity. On the other hand, it is obvious that, with a few exceptions, we are far from a comprehensive understanding of the causes of these diseases. There are three sets of problems.

First, there must be numerous unidentified, possibly interacting, risk factors, some of which may be easier preventable than those already known. Although genetic and perinatal environmental risk factors are coming into the scenario, there is still room for search for risk factors acting in adulthood.

Second, the evidence in most studies are based on study designs with one assessment of the risk factor and its relationship to subsequent disease risk. This kind of evidence raises the question whether changes in the risk factors do lead to corresponding changes in the disease risk, which - in view of unfeasible or very resource-demanding intervention studies - may be addressed in a longitudinal approach, where naturally occurring changes are related to subsequent changes in disease risk.

Third, the variation within populations in the exposure to important risk factors may be so small that studies limited to a single population may be unsuitable to detect the effect of the risk factor. If almost everyone is exposed or exposed to about the same degree, or if only very few in a population are exposed, it may not be feasible to obtain sufficiently large samples for comparisons. For less common chronic diseases in adulthood, particularly rare cancers, the requirements regarding sample size have prohibited identification of risk factors.

h. Longitudinal analysis of disease causes in the prospective studies of adult populations

Aims: Identification, specification and quantification of the relationship between putative long-acting risk factors and incidence of cardio and cerebrovascular diseases, several types of common cancer, non-insulin dependent diabetes, and chronic obstructive lung diseases.

Study population and workplan: The study is using longitudinal analysis of large population-based cohorts of adult subjects assessed one or more times after entry with regard to putative disease causes, and followed up for several years with regard to disease development. Three cohorts will be included: the Glostrup Population Studies (12,000 men and women surveyed in multiple subcohorts since 1964), the Copenhagen Male Study (5,000 men surveyed since 1970-71), and the Copenhagen City Heart Study (14,000 men and women surveyed since 1976-78). At each of the examinations, the members of the cohorts have undergone a comprehensive health and putative risk factor screening, and register-based follow-up has been obtained by record linkage with the Central Person Register, the Death Certificate Register, the Somatic Hospital Discharge Register, and the Danish Cancer Register.

By integrating and harmonizing the cohorts, it will be possible to estimate the relationship between the putative disease causes and the subsequent incidence of disease, and to specify the risk function with regard to interactions between putative disease causes, duration and changes of the risk factors, stability over age and calendar time.

i. Case-control study of occupational causes of rare cancers

Aims: To look for new potential carcinogens of importance for the development of rare cancers in European workplaces.

Study population: A European collaborative effort shall ensure the enrolment of a sufficient number of cases for the study. Seven cancer sites have been selected that may have a possible occupational etiology, and which have all so far been insufficiently studied because they are so rare. The cancer sites are the small intestine, gall bladder, thymus, bone, male breast, eye, and skin (mycosis fungoides). At least 150 cases of each tumour and a total of more than 800 common controls will be included.

Workplan: Information on occupational exposures will be collected by face-to-face interviews using a structured questionnaire. Exposure assessments will be performed with the

assistance of experienced hygienists and toxicologists. Particularly, the potential carcinogenic effect of exposure to welding fumes and welding light, occupational exposures with oestrogenic effects, exposure to magnetic fields and solvents/pesticides will be evaluated.

Evaluation of p53 deactivation in tumour tissue will also be carried out. This is a frequent genetic change in human cancers. Interesting associations between an occupational exposure and cancer found by means of the questionnaire information will be explored further by analysing mutations in exons 5-8 by PCR-amplification and DNA sequencing. Comparing exposures between persons with either activated or deactivated p53 tumour suppressor gene will tell us whether the exposure plays a role through deactivation, or if it interacts with prior genetic damage.

j. European fecundity surveys

Aim: To study variation in fecundity across different European cultures with different sexual norms and large differences in exposures to expected causes of sub-fecundity, such as sexually transmitted diseases and occupational exposures.

Study population and workplan: A European collaborative study shall ensure the collection of base line data from a large number of countries which differ with respect to potential causes of low fecundity. As part of an EC funded concerted action, representative samples of women in the child bearing age have been interviewed in a large number of European countries and in Greenland. Consecutive samples of nullipara pregnant women in several European countries will be examined as part of the same programme. Fecundity is measured as waiting time to pregnancy. The data will be used to examine the possible association between fecundity and different exposure and life-style variables.

IIc. MILESTONES

The activity in the research center will have milestones at two levels:
The building up and functioning of the centre, and within each project or set of projects.

Milestones at the centre level

Year 1: Practical organization of the centre, purchase of equipment, appointments, establishment of internal routines of the central unit and modes of collaboration between the central unit and the participating research units. Start of seminars with national or

international guest speakers. Inclusion and continuation of the current research activities of the participating research units. Finalizing the detailed protocols of the new research activities of the center. Planning of postgraduate research courses.

Year 2: Identification of common specific aims and overlap in these research activities of the participating research units and subsequent integration. Implementation of the planned new research activities. Running postgraduate research courses and establishing a PhD programme.

Year 3-5: Completed integration of participating research units and implementation of research activities and continuation of research training and PhD programmes in the centre.

Milestones at the project level

At the project level, common milestones can be defined by the stages of the research activity, but the time schedule differs between projects. Moreover, the stages are often not clearly separated and return to previous stages frequently takes place.

The current research projects are at the time of the start of the centre at very different stages, some being at the starting point and others being just before publication. This particular pattern of activities implies that a number of original publications will be submitted and appear every year from the start of the centre.

III RESOURCES NEEDED TO ACHIEVE THE GOALS

Organization of the centre and budget justification

Organizing a collaborative network will secure optimal utilization of manpower, resources and facilities already available in the existing units, and thereby minimize the extra demands for the centre. The central unit will be the workplace of all coordinating activities of the research centre. It will contain offices, meeting rooms, archives, computers, and biobank facilities.

The central unit will from the begining host some of the proposers full time, others part time, as well as the research staff, and guest researchers. It is important to maintain the contact to the well-established Ph.D. training programmes and the laboratory facilities (mainly in toxicology and molecular epidemiology) available in Aarhus. Therefore, the centre leader (Jørn Olsen) will initially keep his position at the Steno Institute of Public Health at the Aarhus University (40% time). However, an increasing percentage will probably be allocated to the central unit as the centre develops.

An essential part of the function of the central unit is the frequent, regular, thorough discussion among all participating researchers of new plans for research projects, of status reports of current projects particularly during the statistical analysis phase, of results of the analyses, and of draft manuscripts. Monthly seminars will be held to which Danish and foreign experts are invited speakers.

Budget

In addition to the resources expected to be available for the centre from the basic support of the proposer's research units and previously received research grants, the demands of the centre fall into two categories: a) personnel, running expenses for the central unit; and b) data collection expenses. The budget for this proposal represents the estimated annual costs which amounts to DKr 9,770,000 or app. £ 1,000,000 or US$ 1,500,000. The budget assumes that the resources available in the participating research units can be transferred to the centre to the extent that they are given for projects included in the centre. The estimates for data collection are arbitrary and will be currently modified according to the needs for the project activities. We expect the housing of the research centre to be covered by the hosting institution. Purchase of equipment for the central unit the first year will be deducted from the budget for data collection.

		in 1000 D.kr.
Personnel		
Centre leader, professor (60% time)	1	360
Post-doc fellows	4 (a)	1,800
Statisticians	3	1,000
Ph.D. students	4 (b)	1,000
Programmer	1	250
Research assistants	4	400
Secretaries	2	400
Technical assistant	1	160
Total		**5,370**
Running expenses		
Guest seminars/workshops, guests and travel		500
Administrative costs		300
Routine office supplies		200
Maintenance and renewal of equipment		300
Maintenance of biobanks		100
Total		**1,400**
Budget for data collection		
Design and printing of questionnaires		150
Extracts from person registers		100
Mailing of questionnaires		250
Telephone or on site (home, workplace) interviews		400
Health examinations and biological sampling		900
Computerized register linkage		300
Manual retrieval of information in archives		400
Laboratory analysis of biological samples		500
Total		**3,000**
Total annual costs		**9,770**
Equipment (this is deducted from this budget the first year)		
Computers and supporting equipment		600
Software for data management and statistical analysis		100
Optical reading machine		200
Security system		100
Photocopy and fax machines		100
Equipment for preparing samples for the biobank		200
Total		**1,300**

a) Two guest researchers;
b) In total 12 expected at any time, 4 paid by the programme.

IV QUALIFICATIONS OF THE RESEARCH GROUP

General qualifications

The proposers of the centre have been active researchers in analytical epidemiology for many years, and they have published their results in leading international scientific journals (see the enclosed lists of publications). They have substantial experience in establishing and being responsible leaders of new research groups and in research collaboration, both at the national and international level. They bring together a multidisciplinary background in education, postgraduate training, and specific areas of research interest, thereby supplementing each other.

The group carries considerable experience in institutional, organizational, and administrative leadership, in peer reviewing grant proposals for both Danish, foreign, and EC granting agencies, in peer reviewing of papers for international scientific journals and doctoral dissertations for faculties, in evaluation of applicants for research positions including Danish and foreign professor chairs, in provision of scientific advice on consultative basis and as members of advisory boards, in pre- and postgraduate research education both in supervision and teaching.

Jørn Olsen

Jørn Olsen is 46, became M.D. in 1973/74 and Ph.D. in 1980 at the University of Aarhus. After a short clinical training, he has since 1975 followed an academic research career at the Universities of Aarhus and Odense. In 1984 he was appointed professor of epidemiology and social medicine at the University of Aarhus. He has been teaching epidemiology and biostatistics at several postgraduate courses in Denmark and abroad, is faculty member of The European Educational Programme in Epidemiology in Florence, has been guest lecturer at several distinguished foreign universities, and has edited an international textbook in epidemiology. He is editor or board member of six scientific journals and regular reviewer for several others. He is or has been member of several EC research groups and advisory committees, and has been member of the Danish Medical Research Council since 1985. His main research interests have been in occupational, perinatal, cancer, and AIDS epidemiology, screening and social medicine. He has been active in initiating epidemiologic research in Denmark and other European countries and has extensive experience in research management.

Mads Melbye

Mads Melbye is 37, became M.D. in 1984 and Dr.Med.Sci. in 1988 at the University of Aarhus. Except for a few years of clinical training, he has held research positions in epidemiology at institutions run by the Danish Cancer Society in Aarhus and Copenhagen and became associate head of Department of Epidemiology at the State Serum Institute in 1991. He has been visiting scientist for prolonged periods at the National Cancer Institute in the U.S.A. and has been on several scientific expeditions in Greenland and Africa. In 1992 he received a 5-year grant as MRC professor in infectious disease epidemiology and was appointed as head of the Epidemiology Research Unit at The State Serum Institute. He has been guest lecturer in several countries and editor of an international handbook on AIDS. He is board member of two scientific journals and reviewer for many other journals. He is or has been member of a number of EC and WHO research groups or advisory committees. His research has focused on infectious disease epidemiology (mainly HIV/AIDS), and virus-induced cancers.

Thorkild IA Sørensen

Thorkild IA Sørensen is 47, became M.D. in 1971, and Dr.Med.Sci. in 1983 at the University of Copenhagen. He has extensive clinical training, first in surgery, interrupted by a 4-year position as assistant professor, then in internal medicine. He is authorized as specialist in medicine and in hepatology, became associate professor in internal medicine in 1984, acting chief physician in 1985 and department chairman in 1988 at the Hvidovre University Hospital, Copenhagen. In 1989 he received a 5-year grant as MRC professor in clinical epidemiology, and he became director of the Institute of Preventive Medicine at the Copenhagen Health Services in 1993. He has considerable pre- and postgraduate teaching experience, and has been visiting professor at the University of Pennsylvania since 1989. He is board member of four scientific journals and reviewer for many other journals. He has been member of a number of Danish, foreign and EC-related scientific committees and advisory boards, and chairman of the scientific committee of the Danish Cancer Society and of the research council of the Copenhagen Health Services. The research interests have been clinical research, trials and epidemiology of hepatic and gastrointestinal diseases, and clinical and genetic epidemiology of body weight and of general mortality.

Peter Aaby

Peter Aaby is 48, became M.S.C. in social anthropology in 1974 and Dr.Med.Sci. in 1988 at the University of Copenhagen. He has held positions as researcher and lecturer in ethnological institutes at the Universities of Copenhagen and Uppsala, and as social scientist in Guniea-Bissau under the auspices of national aid programmes. In 1991, he was appointed by the Dan-Church-Aid as director of the Evaluation and Research Component of the Primary Health Care Project in Guinea-Bissau. He has been guest lecturer in several countries, and member of scientific and advisory committees under WHO and International Union for the Study of Populations. He has spent a great part of his career doing research field work in developing countries, primarily in Guinea-Bissau. His research has mainly dealt with determinants of transmission of and prognosis after infections and effects of vaccinations, particularly for measles, polio, retrovirus infections, whooping cough, tetanus, and diarrhoea.

V FULFILMENT OF GRANTING CRITERIA

The following chapter summarizes the aspects of the proposed centre and research plan which meet the essential criteria set up by the Foundation.

Postgraduate research education

The proposed research centre will offer a comprehensive postgraduate research education in analytical epidemiology. The programme will be integrated with corresponding components of the research education offered at the Danish Universities and coordinated with other national and international activities in the field. The educational programme will encompass 12 positions for Ph.D. students. The selected Ph.D. students will be offered participation in the core research activities of the centre and will be allocated two supervisors one of whom will be one of the proposers of the centre. Basic as well as advanced postgraduate courses open also for Ph.D. students and other young researchers from other disciplines will be set up every year. Monthly open seminars with invited experts from Denmark or abroad will be held.

International attractiveness and impact

The combination of the excellent opportunities for epidemiological research in Denmark

and the high-level quality and quantity of research being conducted in the centre, will undoubtedly make the centre an attractive working place for both senior and junior epidemiologists from abroad. Several of the ongoing or planned research projects cannot be satisfactorily performed in other countries because of less optimal or nonexistant conditions elsewhere. Therefore, the results will be unique and a priori have international impact.

Relevance for Denmark

The proposed centre and research plan will be of relevance for Denmark in several respects: a) the outcome of the research project contributes to the scientific rationale for and to the priority setting of preventive actions in the society and the health services; b) by increasing the utilization of the many information systems in Denmark, the processing and quality control of these systems will be increased; c) the plan meets international expectations in the research community about proper and open utilization of the special opportunities for epidemiological research.

Level of Danish epidemiological research and contribution of the centre

The recent international evaluation of Danish epidemiological research indicated that it is of high level, both regarding quality and quantity. However, there is an obvious lack of concentrated investment in analytical epidemiology as proposed in this centre. It is likely that the research activity in the centre will stimulate the general interest and awareness of analytical epidemiology, which may add new dimensions to the research or even alter the research direction in other settings, both in epidemiological research units as well as in research units of related disciplines. The proposed research training programmes will produce candidates with expertise in epidemiology who will contribute to the research environment in other institutions.

Collaboration with other Danish Research Institutions

The particular structure of the proposed centre secures direct collaboration with the host institutions of the proposer's original research units at Aarhus University, the State Serum Institute, and the Copenhagen Health Services. Of particular importance is the continuation of an already established close collaboration with the Danish Cancer Register and the Biostatistical Research Units at the Universities of Aarhus and Copenhagen. The proposers have connections or active collaboration with almost every research unit in Denmark where

epidemiological research is being conducted.

International collaboration

Several of the current research projects as well as the planned projects involve international collaboration, both in the United States, in several European countries within and outside the European Community, and in some developing countries. Some of the projects are parts of projects that are either sponsored by or submitted for support from the European Community.

The proposers have close contact to a large number of researchers from abroad, but the most important are: *Professor Hans-Olov Adami*, Cancer Epidemiology Unit, Uppsala University, Uppsala, Sweden; *Dr. D. Baird, Director A. Wilcox*, NIEHS, Research Triangle Park, NC, U.S.A; *Professor David Barker*, MRC Environmental Epidemiology Unit, Southampton, UK; *Drs. W.A. Blattner, R. J. Biggar, J. J. Goedert, Robert C Gallo*, National Cancer Institute, USA; *Professor Charles du V. Florey*, Ninewells Medical School, Dundee, Scotland; *Professor Sander Greenland*, Department of Epidemiology, UCLA, Los Angeles, USA.*Professor A. Hofman*, Department of Epidemiology, Erasmus University, Rotterdam, The Netherlands; *Professor Sarnoff Mednick*, Social Science Research Institute, University of Southern California, Los Angeles, USA; *Dr. Joel Palefsky*, University of California, San Francisco, USA; *Dr. Max Parkin*, IARC, Lyon, France; *Director, Dr. Jaap Seidell*, Department of Epidemiology, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands; *Dr. Francois Simondon*, ORSTROM, Dakar, Senegal; *Professor Albert J Stunkard*, Department of Psychiatry, Obesity Research group, University of Pennsylvania, Philadelphia, U.S.A; *Dr. Hilton Whittle*, MRC Laboratories, Fajara, The Gambia;

VI REPORTING AND PUBLICATION POLICY

All major papers presenting the results of the centre will be submitted for publication in international peer-reviewed scientific journals. The results of the research will be presented as soon as possible at national and international scientific meetings and will be made available for the authorities of the health services.

Bilag 4

Projekter, hvor der er givet økonomisk støtte

Fond	Dato	Projektets titel	Ansøger(e)	Bevilget beløb	Anmærkninger
Sygekassernes Helsefond	26.01.1995	Rygning under graviditet, barnets udvikling og sjældne graviditetsudfald	**Tine Brink Henriksen** JO	kr. 150.000	
Sundhedsstyrelsen	18.07.1995	Alkoholforbrug i graviditeten	**Jørn Olsen** AMN, Morten G.	kr. 865.000	
Apotekerfonden af 1991	07.04.1995	Utilsigtede virkninger ved brug af lægemidler i graviditeten	**Jørn Olsen** HTS	kr. 2.238.000	
Novo Nordisk Fonden	28.04.1995	Betydningen af n-3 fedtsyrer indtaget under svangerskab for svangerskabets forløb og barnets udvikling og helbred: et delstudie af det nationale fødselskohorteprojekt	**Sjurdur F Olsen** JO	kr. 50.000	
March of Dimes Birth Defects Foundation	26.02.1996 07.05.1996	1. Dietary marine n-3 fatty acids during pregnancy in relation to preterm delivery, fetal growth retardation, preeclampsia, and associated complications 2. Psychosocial stress in pregnancy and rare adverse pregnancy outcome	**Sjurdur F Olsen** JO **Jørn Olsen** Morten Hedegaard	USD 54,945 USD 60,000	
Apotekerfonden af 1991	26.01.1996	Oprettelsen af den biologiske bank til projektet *Bedre sundhed for mor og barn*	**Mads Melbye**	6 mio.kr.	
Aage Louis-Hansens Mindefond	06.12.1995	Betydningen af n-3 fedtsyrer indtaget under svangerskab for svangerskabets forløb og barnets udvikling og helbred: et delstudie af det nationale fødselskohorteprojekt	**Sjurdur F Olsen**	kr. 50.000	

Projekter hvor der foreligger en protokol

Projektets titel	Ansøger(e)	Indsendt	Bemærkninger
Graviditas prolongata - En epidemiologisk undersøgelse af årsager og risici	Annette Wind Olesen	marts 1996	Projektforslag baseret på lokale data
Præ- og postnatale prædiktorer for kolik (data fra Ringkøbing amt)	Charlotte Søndergaard		Projektforslag baseret på lokale data
Tandforholdene hos mor og barn i et longitudinelt perspektiv	Lisa Bøge Christensen og Poul Erik Petersen	16.04.1996	
Twins in the Danish 100,00 birth cohort study	Kaare Christensen	1994	
Congenital malformations in boys	Niels E. Skakkebæk, Katharina Maria Main	29.05.1996	
Testicular development in boys: is there a role for inhibin B	Niels E. Skakkebæk, Katharina Maria Main, Anna-Maria Andersson	29.05.1996	
Danske børnefamiliers sociale netværk.	Chirstin Plate	03.06.1996	
Fordeling af sundhedsplejerskebesøg på familier i et brugerperspektiv	Anne Salter	03.06.1996	
Incidens og risikofaktorer for 2. trimester abort og ekstrem tidlig fødsel	Anne-Marie Nybo Andersen, Mads Melbye	26.09.1995	
Copenhagen Prospective Study on Asthma in Young Children	Hans Bisgaard, Mads Melbye, Peter Aaby	23.02.1996	
Kostindtag under graviditet i relation til risiko for børnecancer: et delstudie under Den nationale fødselskohorte	Sjurdur F Olsen, Jørn Olsen, Per Kragh Andersen, Kim Overvad, Anne Tjønneland, Walter Willett, Matthew Gilman	15.02.1996	
Betydningen af kostindtag under graviditet for 'programmering' af hjerte-kar-sygdomme og hertemisdannelser hos fosteret: et substudie under Den nationale fødselskohorte	Sjurdur F Olsen, Jørn Olsen, Per Kragh Andersen, Kim Overvad, Anne Tjønneland, Walter Willett, Matthew Gillman	29.02.1996	
Betydningen af moderens kost under graviditeten for forekomsten af alvorlig sygelighed hos mor og barn: En prospektiv undersøgelse blandt 100.000 gravide	Sjurdur F Olsen, Jørn Olsen, Kim Overvad, Anne Tjønneland, Katharina Main, Niels E Skakkebæk, Walter Willett, Matthew Gillman, Prakash Shetty, Jane Pryer, Dave Leon	30.07.1996	
Arbejdsmiljø og reproduktionsskader	Jørn Olsen	10.04.1995	
Gene-environment interaction in facial clefts	Kaare Christensen, JC Murray, B Nørgaard-Pedersen, Jørn Olsen, Mads Melbye	27.09.1995	

Projekter i idéfasen, hvor der eventuelt foreligger en skitsemæssig protokol

Projektets titel	Ansøger(e)	Indsendt	Bemærkninger
En undersøgelse af relationen mellem hyppige tilfælde af mellemøresygdom (akut og sekretorisk otitis media) og cognitiv udvikling	Jørgen Lous	17.02.1994	
Prospektiv epidemiologisk undersøgelse af sammenhængen mellem maternelle virusinfektioner og forekomst af schizophreni i voksenalder	Merete Nordentoft	05.08.1994	
- Navlesnorsprøver tages fra til HLA-typning. I første omgang types for IDDM disponerende og protektive alleler. - Årlig prøve til bestemmelse af GAD antistoffer. - Registrering af forekomst af IDDM i kohorten via incidensregistret.	Flemming Pociot og Birgitte K. Michelsen	07.03.1995	
The societal and personal problem of schizophrenia	Fini Schulsinger og Sarnoff Mednick	04.08.1995	
The European newborn-IDDM project	Karsten Buschard	17.10.1995	
Determinanter for perinatal hypoxisk iskæmisk encefalopati samt cerebral parese	Hans C Lou, Ole Pryds, Peter Uldall	22.02.1996	
Identifikation af exogene determinanter til hyperkinetisk syndrom samt identifikation af tidlige symptomer på hyperkinetisk syndrom	Jente Andresen, Hans C Lou, m.v.	22.02.1996	
Identifikation af psykosociale faktorer og andre determinanter til lav hjernevækst bedømt ved hovedomfangsmålinger	Hans C Lou, Dorthe Hansen, Merete Nordentoft, Ole Pryds	22.02.1996	
Betydningen af præ- og postnatale faktorer for udvikling af barnets personlighed	**Erik Lykke Mortensen**, Jente Andresen, Jerome Kagan, Thorkild IA Sørensen, m.fl.	29.05.1996	
Betydningen af præ- og postnatale faktorer for udvikling af DAMP	**Jente Andresen**, Hans Lou, Erik Lykke Mortensen, Thorkild IA Sørensen, m.fl.	29.05.1996	
Betydningen af præ- og postnatale faktorer for risiko for udvikling af misbrug og afhængighed	**Erik Lykke Mortensen**, Jente Andresen, Thorkild IA Sørensen, m.fl.	29.05.1996	
Betydningen af præ- og postnatale faktorer for udvikling af svær mental retardering	**Margareta Mikkelsen**, Jente Andresen, Erik Lykke Mortensen, Thorkild IA Sørensen, m.fl.	29.05.1996	
Betydningen af præ- og postnatale faktorer for risikoen for psykoser	**Fini Schulsinger**, Jente Andresen, Sarnoff A Mednick, Erik Lykke Mortensen, Thorkild IA Sørensen, m.fl.	29.05.1996	
Betydningen af præ- og postnatale faktorer for vækst og fedme	**Thorkild IA Sørensen**, Berit L. Heitman, Kim Fleischer Michaelsen, Sjurdur F Olsen, m.fl.	29.05.1996	
Betydningen af præ- og postnatale faktorer for udvikling af risiko for hjerte-karsygdomme (dog ej gravides kost)	**Thorkild IA Sørensen**, Kim Fleischer Michaelsen, Sjurdur F Olsen, m.fl.	29.05.1996	

Projektets titel	Ansøger(e)	Indsendt	Bemærkninger
Præ- og postnatale ekspositioners betydning for udvikling af børneleukæmi	**Mads Melbye** et al.	11.06.1996	
Intrauterine infektioners betydning for sanseorgansdefekter	**Mads Melbye** et al.	11.06.1996	
Intrauterine infektioners betydning for udvikling af juvenil diabetes	**Mads Melbye** et al.	11.06.1996	
Intrauterin infektion med parvovirus B19 og betydning for barnets senere udvikling.	**Mads Melbye** et al.	11.06.1996	
Uspecifikke effekter af vaccinationer. Er vaccinationer forbundet med eller virker beskyttende i forhold til anden sygelighed	**Peter Aaby**, Mads Melbye	16.06.1996	
Infektionernes og vaccinationer betydning for udvikling af allergi	**Peter Aaby**, Mads Melbye	16.06.1996	
Skadelige og gavnlige langtidseffekter af infektioner i løbet af de første 18 måneder af livet; herunder sygelighed som determinant for senere sygelighed og infektionsalderens betydning for kroniske sygdomme	**Peter Aaby**, Mads Melbye	16.06.1996	
Sygelighed blandt tvillinger: har kønslighed eller kønsforskel en betydning for alvorligheden af infektioner?	**Peter Aaby**, Mads Melbye	16.06.1996	
Betydning af længden og intensiteten af amning for senere udvikling af allergi	**Peter Aaby**, Mads Melbye, Kim Fleischer Michaelsen	16.06.1996	
Betydningen af familiestruktur og boligforhold for sygelighed	**Peter Aaby**, Mads Melbye	16.06.1996	