EPIDEMIOLOGY FOR STUDY OF PUBLIC HEALTH VOL.2

METHODS IN EPIDEMIOLOGY
EPIDEMIOLOGY OF CHRONIC CIVILISATION DISEASES AND PREVENTION

Edited by

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EPIDEMIOLOGY FOR STUDY OF PUBLIC HEALTH VOL.2
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- Biology and Genetics for Public Health, Pharmacology in Public Health
- Basics of Clinical Microbiology and Immunology for MPH Students
- Environmental Health - Hygiene
- Occupational Health and Toxicology
- Introductory Biostatistics
- Social Medicine
- Health Promotion and Health Communication
- Public Health Ethics - Selected Issues
- An Introduction to Public Health Law
- Healthcare Management
- Information Technologies in Medicine, Medical Information Systems and eHealth
- Management of Information Systems Projects in Transition to Knowledge Management
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PREFACE

Epidemiology is a core of Public Health. The first part of presented book for students of Public Health is focused on epidemiologic methods (descriptive, analytic, experimental studies) used in public health. Epidemiology, through applications of epidemiologic methods in the study of health problems is fundamental in determination of the main health problems but also in development, adoption, and implementation of health policy, prevention and health practice through long-term epidemiologic surveillance.

The rising prevalence of type 2 diabetes mellitus is associated with rapid cultural and social changes, ageing populations, increasing urbanization, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioral patterns.

In the last fifty years public health has to turn attention and reallocation of resources to chronic non-communicable diseases research, to recognize the most risk factors associated with chronic health impairment and prepare longtime prevention to these diseases with multifactorial etiology. Therefore the second part of this textbook is intended for recognizing occurrence, risk factors and characteristics of the main chronic diseases (cardiovascular diseases, cancer, diabetes, chronic lung diseases) with the highest burden and mortality rates.

Current global mortality from non-communicable diseases (NCDs) remains unacceptably high and is increasing. Out of an estimated 55 million people who died worldwide in 2011 these diseases cause 36 million deaths comparing to 31 million in 2000. Cardiovascular diseases, cancer, diabetes and chronic lung diseases were mainly responsible for about 75% of all deaths globally in 2011, up from 60% in 2000. Non-communicable diseases also dominate in the list of the top disease burden in developed countries: unipolar depressive disorders and ischemic heart disease are the leading causes of disability-adjusted life years (DALYs) lost.

The 2008 to 2013 Action Plan for the Global Strategy for the Prevention and Control of Non-communicable Diseases was designed to provide WHO Member States, and the international community guidance for the surveillance, prevention and management of NCDs. Continuing efforts in updated Action Plan 2013-2020 were developed to concrete global targets for 2025 with the aim to attain a 25% reduction in premature mortality from NCDs.

In terms of number of deaths, 26 million (nearly 80%) of the 36 million of global NCD deaths in 2011 occurred in low- and middle-income countries. In terms of proportion of deaths that are due to NCDs, high-income countries had the highest proportion (87% of all deaths) followed by upper-middle income countries (81%). The proportions were lower in low-income countries (36%) and lower-middle income countries (56%).

Cardiovascular diseases killed nearly 17 million people (47.2%) in 2011, comparing to 15 million victims in 2000. In 2011 7 million people died of ischemic heart disease and 6.2 million from stroke. Lung cancers (along with trachea and bronchus cancers) caused 1.5 million (2.7%) deaths in 2011, up from 1.2 million (2.2%) deaths in 2000. Similarly, diabetes caused 1.4 million (2.6%) deaths in 2011, up from 1.0 million (1.9%) deaths in 2000.
These premature deaths are largely preventable by governments implementing measures which reduce risk factors for NCDs and enable health systems to respond. Behavioral risk factors (including tobacco use, physical inactivity, unhealthy diet and the harmful use of alcohol) are associated with four key metabolic and/or physiological changes – raised blood pressure, increased weight leading to obesity, hyperglycemia and hyperlipidemia. Tobacco use is a major cause of many of the world’s top killer NCD diseases, in total, tobacco use is responsible for the death of about 1 in 10 adults worldwide.

Once public health priorities have been established through monitoring and investigation of non-communicable diseases in the community, educational activities that prevent occurrence of these health problems and promote improved health should be disseminated. Components in this service include: both the availability of health information and educational resources and the presence of health education and health promotion programs designed by professionals of public health.

The authors hope that this book will help and guide MPH students to better prepare for their study and practice in the field of Public Health by using epidemiological methods and general principles of epidemiology of non-communicable diseases for their control and prevention.
1 METHODS IN EPIDEMIOLOGY

1.1 INTRODUCTION TO METHODS IN EPIDEMIOLOGY

The most classical way of classifying epidemiological studies is that the studies may be descriptive in nature (describing the frequency or characteristics of events) or analytic (testing relationships between common traits and outcomes).

The alternative way of classifying epidemiological studies accounts for the role/control of the researcher/investigator over the study. Observational studies refer to the broad class of epidemiological study designs characterized by the fact that exposure is not assigned by the investigator. Rather, the investigator passively observes as nature takes its course. In experimental studies the researcher has control over the circumstances from the start, means that investigator actively assigns exposure to an investigated population.

Observational studies can be further subdivided into descriptive and analytical studies. Descriptive observational studies are designed to collect information on the distribution of disease patterns in terms of the characteristics of person, place, and time but are not designed to test a causal hypothesis. Analytic observational studies assemble a population for study for the purposes of testing a causal hypothesis concerning the relationship between exposure or risk factors and disease (Tab 1.). But in general, analytic studies include both observational designs (case-control studies, cohort studies, etc.) and in some occasions experimental designs (the randomized controlled trial, etc.). In an analytical study, the epidemiologist relies on comparisons between groups to determine the role of various risk factors in causing the problem. An important overlap in both classifications therefore exists.

Epidemiological studies can be classified further according to the direction of inquiry as either prospective (cohort studies) or retrospective (case-control studies).

In a prospective (forward - looking) study disease free subjects who are exposed (or with risk factor) and non-exposed people (or without risk factor) are followed up and compared with respect to the subsequent development of the disease/outcome under study. Prospective studies collect data forwards in time in order to examine the etiology of disease (observational study) or to assess the effectiveness of an intervention (experimental study). In a retrospective (backward - looking) study subjects with the disease are compared with subjects without the disease (or risk factor), to determine whether they differ in their past exposure to the (hypothesized) causative factor or risk factor.
Table 1. Classification of epidemiological studies

<table>
<thead>
<tr>
<th>Epidemiological studies</th>
<th>Methods in epidemiology</th>
<th>Types of studies</th>
<th>Direction of inquiry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational</td>
<td>Descriptive</td>
<td>Populations (correlational, ecologic, aggregate studies)</td>
<td>retrospective</td>
</tr>
<tr>
<td>Observational</td>
<td>Descriptive</td>
<td>Individuals (case-report, case series)</td>
<td>retrospective</td>
</tr>
<tr>
<td>Observational</td>
<td>Analytic</td>
<td>Cross-sectional</td>
<td>retrospective</td>
</tr>
<tr>
<td>Observational</td>
<td>Analytic</td>
<td>Case-control</td>
<td>retrospective</td>
</tr>
<tr>
<td>Observational</td>
<td>Analytic</td>
<td>Cohort</td>
<td>prospective (may be also retrospective)</td>
</tr>
<tr>
<td>Experimental</td>
<td>Experimental</td>
<td>Clinical trial, Field-Community trial</td>
<td>prospective</td>
</tr>
<tr>
<td>Surveillance</td>
<td>Surveillance</td>
<td>Long-term collecting data, analysis, leading to measures</td>
<td>Continually from past to future</td>
</tr>
</tbody>
</table>

Analytical studies are usually performed on a sample of population, not on entire population. This group of the population representing current demographic structure must be relatively identical a representative sample of the basic population in the sense of homogeneity, characteristics, criteria of selection and size. The studies are performed thus more simply and quickly, with economic benefit allowing to infer results to the whole population.

Epidemiology as an extremely diversified branch of medicine uses different experimental studies, such as a wide variety of laboratory-based experiments (on animals, microbial cultures, etc.) in preclinical tests on new vaccines, disinfectants, further clinical trials testing efficacy of new drugs, but also large well designed community or field trials for successful implementation of large-scale control measures on population level (community trials).

Epidemiologic surveillance is the ongoing and systematic collection, analysis, interpretation and distribution of data about a disease or health conditions.

Simple algorithm how to recognize what type of design is used for a study is shown in Figure 1. This is important as the design of a study determines types of inferences that can be drawn from it. Given the strengths and limitations of each design each type of epidemiologic study simply represents a different way of harvesting information and answering specific research questions.
Figure 1. Algorithm for classification of types of clinical research


References:

1.2 DESCRIPTIVE EPIDEMIOLOGY

Descriptive epidemiology deals with the distribution of diseases and with health associated conditions in populations in relation to time, place and person’s characteristics. It describes and studies the circumstances under which they occur in a population.

1.2.1 Scope and aims of descriptive epidemiology

Descriptive epidemiology is the oldest and primary epidemiological working method. Initially it was used in epidemiology of infectious diseases. It has been the observation and description of outer manifestations of the epidemic process – the occurrence, spread and consequences of communicable diseases in populations. Its scope has been later extended also to the study of occurrence of non-communicable diseases and other with health associated conditions.

Descriptive epidemiological method provides a way of collecting, organizing and analyzing information from different health data sources to monitor disease and health distribution and trends in populations, in order to understand variations in disease occurrence and frequency over time, geographically, and with respect to personal or host characteristics. This makes possible to forecast future development and planning health care capacities and resources.

Descriptive method is important in searching for possible explanations by generating hypotheses about the determinants of health and disease.

In this way, descriptive epidemiology provides the important starting point for analytic epidemiology, which formally tests associations between potential determinants and risk factors and health or disease outcomes.

Specific tasks of descriptive epidemiology are the following:
- monitoring and reporting on the health status and health related behaviors in populations;
- identifying emerging health problems;
- alerting to potential threats – emergence of diseases, disasters, bioterrorism;
- establishing public health priorities for a population;
- exploring potential associations between risk factors and health outcomes in order to generate hypotheses about the determinants of disease.
- evaluating the effectiveness of implemented measures, programs and strategies.

Epidemiologic observations and descriptions of disease and with health associated conditions and their distribution on whole population level or in specified parts of populations are oriented on three basic determinants, time, place and characteristics of persons.

The occurrence is generally presented quantitatively, preferably by indicators such as incidence, prevalence, mortality or case fatality rates, age and gender specific rates, seasonality and others.

1.2.2 Temporal distribution (distribution in time)

The occurrence of diseases and with health associated problems has been followed through different time periods along with their epidemiologic importance. If indicators of a disease, infectious or noninfectious, are assessed in different time intervals, mainly if the data are graphically presented, we can observe fluctuations of the intensity of disease occurrence – larger or smaller peaks and drops of time curves. Over time, the incidence of diseases may undergo several types of variations, which may be as follows:
Regular (periodic) fluctuations

Many diseases are observed to undergo regular changes in disease frequency over a shorter or longer followed time period (commonly one calendar year or one-two decades, respectively). Regular fluctuations during a one year period with peaks and declines linked to seasons of the year are seasonal variations - another term used for this phenomenon is seasonality.

Different mainly “external” factors - physical (climatic conditions, weather, temperature, humidity), - biological (activity of insects and other arthropods which are disease vectors, pollen in the atmosphere associated with attacks of asthma), - social (beginning of school attendance, higher cumulation of people in winter, spending more time in nature) contribute to more or less typical seasonal occurrence.

For example typical rise in frequency of influenza cases in cold season (higher indoor exposure), that of intestinal infections mainly in hot season (supporting transmission of food-borne infections), tick-borne encephalitis in spring and autumn (summer in milder woody regions).

In some chronical diseases there were also found characteristic seasonal variations.

For example the rise in incidence rate of diabetes mellitus type 1 being recorded mainly in winter (analytical studies are under way as to associations with some viral infections).

Seasonal variations in incidence belong to basic epidemiologic characteristics, mainly used in epidemiology of infectious diseases (data routinely presented on monthly or weekly basis).

Several-year fluctuations in a longer time period from years to decades involving periodic changes also termed as periodicity - more or less regular “epidemic“ peaks and drops between them due to some „internal” factors such as collective or herd immunity of the population at risk.

This phenomenon is based on lowered probability of acquiring specific disease (leaving solid immunity) after an epidemic, when majority of susceptible individuals developed antibodies and cannot spread the infection.

For example in diseases of childhood leaving solid, up to lifelong immunity, rise in incidence occurs after several years intervals (generally 3-4 years) of the lower frequency of cases – this being conditioned by the gradually increasing number of infants and toddlers without immunity to the relevant disease (varicella, scarlet fever, before introduction of mass vaccination also measles, mumps, rubella, diphtheria, pertussis, etc.).

Cyclic fluctuations with rises in disease occurrence characteristic for some zoonoses (e.g. tularemia, leptospirosis), associated with population dynamics of reservoir animals, mainly wild rodents (4-5 year or longer intervals between years of overpopulation with epizootic outbreaks), followed frequently by epidemics.

Irregular (nonperiodic) fluctuations in disease frequency and intensity of the epidemic process. These occur as outbreaks or increased disease occurrence caused by different reasons, e.g. in infectious diseases by epidemics and pandemics, in other diseases due to physical or chemical agents, environmental pollutants, accidents, natural disasters, etc.

From infectious diseases, e.g. in influenza, which presents itself generally by periodic fluctuations of the occurrence, the entrance of new antigenic types of viruses (e.g. caused by antigenic shifts) into circulation in naïve (nonimmune) population gives a chance of pandemic spread of the disease over countries and even over continents. Irregular sharp rises in disease incidence due to epidemics of different causes could occur in many other diseases, often diarrheal (e.g. salmonellosis, rotavirus diarrhea, cholera), waterborne outbreaks of viral hepatitis A and E occur e.g. during floods.
Long-term trends of disease occurrence

By means of statistical methods trends of disease occurrence are being counted, and further presented graphically by fitting trend line through the time curve data. Computerized follow-up of trends of disease frequency being indispensable for making prognoses, planning and strategies of control in diseases with mass occurrence and conditions of epidemiological and social importance (HIV, TBC, etc.) on the local, regional and global levels.

Secular trends refer to changes in the occurrence of disease over prolonged period of time such as years. The term usually implies changes in disease frequency that encompass several decades. A decreasing secular trend of an infectious disease is usually the result of specific and nonspecific immunity, an improved health care, hygiene and sanitation among the involved population. Causes of secular trends are often not understood.

For example even prior to the measles vaccination, decrease in morbidity due to this condition was observed in some countries.

From non-communicable diseases e.g. decreasing occurrence of stomach cancer, observed in last decades globally, has been understood only partially. On the contrary, rise in worldwide prevalence of obesity, which has nearly doubled since 1980, is mainly due to known unhealthy life-style changes.

1.2.3 Geographic distribution (place)

Distribution of diseases and with health associated problems on the Earth and their occurrence in different geographic regions belongs to key epidemiologic characteristics. Continuous collection of data on disease occurrence according to administrative regions from subnational up to global level and their evaluation represent fundamentals of descriptive epidemiology. Variations in frequency of different disease manifestations from place to place have long been recognized. Separate disciplines such as geographic medicine or tropical medicine have been created to deal with geographically determined health problems. The different geographical distribution of a given disease may be related to several environmental influences:

Climate – factors as temperature, humidity, winds (direction, velocity), precipitations, etc. are conditions for endemic occurrence of vector-borne diseases, in particular zoonoses with natural foci.

For example the existence of mosquitoes, vectors of severe diseases (malaria, yellow fever dengue) mainly in hot climate zones, a higher specific temperature and humidity are necessary – if inappropriate, conditions are not met, mosquitoes cannot develop and there is no risk of disease transmission in the region; on the contrary global warming can contribute to enlargement of areas favorable to vectors also to former mild climate zones causing e.g. spread of dengue in Mediterranean.

Geological factors determining presence of chemical compounds in water and soil – their deficiency (communities with low level of fluoride in the drinking water have high levels of dental caries, iodine deficiency in the soil causes goiter in people living in such a territory), or their excess (arsenic or lead in water above threshold limit values can cause chronic intoxication, excess of fluoride cause dental fluorosis, etc.).

Urban and rural conditions of living are markedly associated with socioeconomic aspects of living – e.g. in urban populations there is a higher frequency of bronchitis and atherosclerosis, type 2 diabetes mellitus, while in rural populations a higher frequency of zoonoses can be observed.

Epidemiologic and epizootologic measures can contribute to disease elimination or regional eradication - e.g. specific prophylaxis and quarantine of imported animals have led to eradication of rabies in insular countries (Great Britain, Australia).
1.2.4 Personal characteristics

Personal characteristics (characteristics of persons) can exert an important influence on morbidity of some diseases. It is always necessary to analyze particularly:

**Age** - the most important personal characteristic. It is known that some diseases occur predominantly in children (measles, mumps, pertussis, scarlet fever); clinically apparent hepatitis A is more frequent in adults than in children who predominantly suffer from inapparent infections; salmonelloses are 10-15 times more frequent in children under one year of age compared with adults or with the overall population; occurrence of Down’s syndrome in children rises with the age of women in labor.

**Sex (gender)** - is another very important characteristics. For example death rates (mortality rates) from lung cancer are higher in men than in women; women are more frequently affected by goiter, diabetes, cholecystitis, while in men duodenal and gastric ulcer, arteriosclerosis, cardiovascular diseases are more frequent.

**Occupation** – can exert an important specific risk. Pneumoconiosis is more frequently present in miners; dermatomycoses, brucellosis, or so called farmer’s lung in farmers;

Farmer’s lung is an immunologically mediated inflammatory disease of the lung involving the terminal airways associated with intense or repeated exposure to inhaled biologic dusts (mainly exposure to thermophilic *Actinomyces* species).

Occupational cancer can arise from exposure to many substances or certain occupational circumstances such as: asbestos fibers (colorectum, larynx, lung, ovary, pharynx, stomach cancers, mesothelioma), wood dusts (nasopharynx, sinonasal cancers), UV radiation from sunlight (skin cancers), metalworking fluids and mineral oils (bladder, lung, sinonasal, skin cancers), silica dust (lung cancer), diesel engine exhaust (bladder, lung cancers), coal tars and pitches (non-melanoma skin cancer), arsenic (bladder, lung, skin cancers), dioxins (lung cancer), naturally occurring radon (lung cancer), tetrachloroethylene (cervix, non-Hodgkin’s lymphoma, esophagus cancers), work as a painter (bladder, lung), work as a welder (lung cancer, melanoma of the eye), shift (night) work (breast cancer).

The International Agency for Research on Cancer (IARC) lists over 50 substances which are known or probable causes of workplace cancer, and over 100 other possible substances.

**Socio-economic status and lifestyle** of the population may also determine the occurrence of diseases. In people living in poor social conditions e.g. bronchitis, tuberculosis, suicides are more frequent than in rich people and contrarily, in wealthy people myocardial ischemia and some other so called civilization diseases are more frequently found.

Besides these fundamental personal characteristics, there are some others which can influence the occurrence of certain diseases:

**Race and ethnicity** – diabetes mellitus type 2 higher occurrence namely in Pima Indians, Hispanics and black population compared to white one in the U.S.A.,

**Marital status, religion** – studies have shown e.g. historically data on higher occurrence of cervical cancer in married women compared to nuns, etc.

1.2.5 Sources, collection and processing of data for descriptive epidemiology

The study of occurrence of diseases and health related states, epidemic processes and evaluation of epidemiologic work are based on observation of multiple variables. It necessarily includes statistical processing of the data.
\textbf{Statistical methods in epidemiology}

The term \textit{statistics} (from Latin status, or “manner of standing”) can have following meanings:

- \textit{collection of data} presented in certain form, e.g. mortality statistics, morbidity statistics;
- \textit{discipline dealing with application of numerical methods in collecting and presenting data} e.g., in terms of means, standard deviations, rates, ratios, proportions, etc., and their analysis and summarization. This is the scope of so-called descriptive statistics.

Statistical procedures allow also estimating or inferring the characteristic of a larger population from a sample (process of generalization). This is the scope of so-called \textit{inference (analytic) statistics}. The application of statistics in medicine and biology is biostatistics and biometrics.

\textbf{Phases of statistical work}

Statistical observations of a given phenomenon usually includes following four steps:

- \textit{planning} with identification of the study (control) groups, substantiation of criteria (including, excluding), identification of observed signs, conditions of their measurement, etc.
- \textit{collection of data} using several ways - \textit{direct detection} (including observation, epidemiological survey, laboratory examination, health reports, overviews, etc.) - taking \textit{anamnestic data} either by an interview (personal or family history and the like) or using questionnaire.
- \textit{sorting and computing of data} involves revision of data and exclusion of distorted or biased ones, sorting, tabulation, graphic presentation, statistical summarization and analysis (centralized or decentralized),
- \textit{evaluation of results and conclusions}.

Basic component of epidemiologic work being collection of epidemiologically important data, followed by their revision and analysis, for to obtain objective information on disease occurrence and state of health of study populations.

\textbf{Sources of data} for descriptive epidemiology generally involve:

- \textit{demographic data}, collected on a countrywide basis, usually at the decennial census - an official count of a country’s total population, carried out every ten years at around the beginning of the decade. In an interval, estimates are made by mathematic interpolations.
- \textit{health data} and outputs of regular and other reports and medical examinations - incidence and mortality, data based on notifiable birth and death certificates, records on immunization, immune-status surveys, records on medical history, epidemiologic examination, dispensation records, autopsy records, data from questionnaires and other population surveys.

Data are being obtained for purposes of \textit{routine statistics} and for to draw up required \textit{statistical reports of precisely specified contents} (e.g. yearly accounts kept on activity of outpatient diabetes units, activity of outpatient pneumology and phthisiology units, dental care and others), or for purposes of \textit{one-off statistical surveys} with precisely defined targets for specific problem solving, such as implementation of epidemiologic measures.

Data of routine statistics serve for public health and health care purposes among others.

\textbf{Population statistics} are based on \textit{census} - data are collected about the geographical and economic characteristics of the population, and the characteristics of individuals
and households. Certain of these data are commonly used (e.g. for the denominator) in routine health statistics, as medical records (usually providing the numerator in the calculation of rates) contain limited social, economic and geographical information.

**Health statistics** is founded on basic demographic characteristics of the country. Provides mainly data on health status of population, such as overviews on causes of death, disability, sick leave, statistics on hospitalized patients and causes of hospitalization, overviews on compulsory notified diseases, congenital disorders, reports on venereal diseases, drug users, occupational diseases and others. Further health statistics provides data on health service such as e.g. outpatient and inpatient care, network and activity of health establishments etc.

**Social security statistics** - the growth of social security systems has given an insight into the frequency with which different diseases result in absence from work as distinct from general practitioner consultation or hospital admission.

For comparability of data obtained from different groups of population, uniform and correct collection of information, accuracy of terminology, precision of definitions and constituent criteria are of great importance. To be useful, information and data must be true and correctly recorded as they have occurred. Use of erroneous basic information could result in incorrect conclusions and ineffective measures.

**National Health Information Centre (NHIC)** is a state-funded organization, performing tasks in the areas of informatization of health service, administration of the National Health Information System, standardization of health informatics, health statistics, administration of national health registries and administrative registries, provision of information services, etc. NHIC collaborates with institutions such as Statistical Office of the Slovak Republic (SR), the Health Care Surveillance Authority, the Public Health Authority of the SR, the State Institute for Drug Control, the Slovak Academy of Sciences, health care providers, chambers and health professional organizations, health insurance companies and medical faculties, at an international level with the WHO, ECDC, EUROSTAT and others.

NHIC collects and processes selected data on health status of a population, on network and activities of health care providers and other organizations, on health workforce, medical equipment as well as on economy of health service including health care funding provided on the basis of health insurance. The obtained and processed data are provided in the required form, extent and structure to the Ministry of Health of the Slovak Republic (MH SR), the Statistical Office, chief experts of MH SR as well as foreign data users, namely WHO, OECD and Eurostat. NHIC publishes regularly topical publications in the field of health statistics such as statistical overviews, annual reports, quarterly reports and analytical publication.

The **Health Yearbook of the Slovak Republic** - provides statistical overviews of health care service and health status of the Slovak population based on statistical surveys of the health sector. NHIC is responsible for collection, processing and production of the published outputs. Other statistical providers are Regional Public Health Authority in Banská Bystrica and National Institute for Tuberculosis, Lung Diseases and Thoracic Surgery in Vyšné Hágy. The publication also contains demographic statistics processed by the Statistical Office of the Slovak Republic and reporting data from the Health Organization.

**Edition of Health Statistics** offers titles focusing the health status of population and activity of the specialized units according to the type of health care: activity of outpatient diabetes units, cardiology outpatient units, common diagnostic and curative facilities, surgery and one day care, occupational diseases or disease threats, substance dependence - drug user treatment, nephrology care and kidney function substituting treatment, psychiatric care, congenital anomalies, outpatient gynecology units,
outpatient units for children and adolescents, clinical and radiation oncology, dental care, outpatient pneumology and phtisiology as well as dermatology and venerology units.

**Hospitalised Patients Statistic** provides a complex overview of hospitalised patients in institutional healthcare facilities. Statistics of hospitalised patients is a significant source of morbidity surveillance requiring hospitalisation. Data on finished hospitalizations, indicators of length of hospital care, type of treatment, number of dead patients are analyzed according to international disease classification ICD-10, the most common causes of hospitalisation, sex and age of patients.

Analytical Publication Incidence of Malignant Neoplasms in the Slovak Republic contains standard outputs in absolute and relative indicators, referring to incidence of malignant neoplasms within the whole SR and its regions. The basis for analyzed outputs is Report on Malignant Neoplasm and Controlling Report on Malignant Neoplasm of all patients in the Slovak Republic who were diagnosed a malignant neoplasm (C00-C97), carcinoma in situ (D00-D09), neoplasms of uncertain or unknown behavior (D37-D48) or benign neoplasms of central nervous system -CNS (D32-D33) according to ICD-10.

### 1.2.6 System of disease notification

In many countries a system of compulsory reporting of **infectious diseases** has been developed. The physician and other health workers (including laboratory workers) who first diagnose a notifiable infectious disease should report it to the respective Public Health Authority. In Slovakia, reports on occurrence of infectious diseases are collected by Regional Public Health Authorities in an epidemiologic information system (EPIS) and they are weekly sent in electronic form to be centrally computed, statistically evaluated and re-sent to the regional authorities.

**Liability to notify** refers to:
- confirmed cases of the disease, but also suspects of the disease or suspects of the infection, if epidemiologically indicated, deaths of the disease,
- carriership of the infectious agent,
- other diseases (besides the list) and epidemiologically important facts and characteristics in special circumstances, if required by the Public Health Authority or Ministry of Health.

**Diseases transmitted from animals to humans** should be reported through Public Health Authorities also to respective Veterinary and Food Administration, according to valid public health regulations.

Notification systems are usually based on reported cases of diseases classified according to internationally accepted classifications, and provide statistical evaluation of data and feed-back of collected information to relevant authorities.

**Actual ICD-10** (International Statistical Classification of Diseases and Related Health Problems 10th Revision) was endorsed by the Forty-third World Health Assembly in 1990 and came into use in WHO Member States from 1994. ICD is currently under revision, through an ongoing revision process and the release date for ICD-11 is 2017.

Following communicable diseases and health associated issues being mandatory reported in the SR according to legislation. Promptitude of reporting, as can be seen from the list, can play a crucial role in controlling spread of highly contagious diseases:

**List of communicable diseases, suspicions of diseases and carrierships of pathogenic microorganisms mandatory reported in the Slovak Republic**

**Group A**

Diseases and suspicions of diseases reported immediately (by telephone, fax, electronically, personally, through a messenger):
- poliomyelitis, severe acute respiratory syndrome (SARS), smallpox, viral hemorrhagic fevers, measles, avian influenza in humans, unknown infectious etiology syndrome with positive epidemiologic anamnesis

**Group B**

**Diseases and suspicions of diseases reported until 24 hours:**
- acute flaccid paresis, botulism, typhoid fever and paratyphoid (inclusive newly detected carriership), cholera, shigellosis,
- diphtheria, bacterial meningitis and encephalitis, mumps, pertussis, rubella,
- tetanus, rabies, contact or rabies hazard,
- hepatitis type A (VHA), B (VHB), C (VHC), E (VHE),
- tuberculosis,
- typhus, relapsing fever, plague,
- legionellosis,
- acute diarrheal diseases and food poisonings (campylobacterioses, salmonelloses and others)

**Group C**

**Diseases reported until 48 hours:**
- nosocomial infections,
- scabies,
- varicella, herpes zoster

**Group D**

**Diseases reported by positive laboratory finding:**
I. All diseases of groups A and B
II. Sexually transmitted diseases: AIDS, carriership of HIV, gonococcal infections, chlamydia infections, lymphogranuloma venereum, syphilis, trichomoniasis
III. Water-borne and food-borne diseases and diseases with environmental origin: giardiasis, infections caused by enterohemorrhagic E.coli and enteroinvasive E.coli, cryptosporidiosis, leptospirosis, listeriosis (involving carriership), rotaviral infections, salmonellosis, taeniasis, toxoplasmosis, trichinellosis, yersiniosis
IV. Other communicable diseases: Creutzfeldt-Jacob disease (CJD), CJD –new variant
V. Other neuroinfections: viral meningitis and encephalitis
VI. Zoonosis and diseases with natural foci: anthrax, brucellosis, echinococcosis, tick-borne encephalitis, leptospirosis, Lyme borreliosis, ornithosis, psittacosis, Q-fever, tularemia
VII. Severe imported diseases: malaria, yellow fever
VIII. Infections of the skin and mucosa: gas gangrene, trachoma

If the public health impact of the event being serious, the event unusual or unexpected, a significant risk of international spread existent, significant risk of requiring international travel or trade restrictions present, the event shall be notified to WHO under the *International Health Regulations* IHR (2005) and 2nd ed. WHO 2008.

**Specific events, detected by national surveillance systems, liable to reporting to WHO:**

* A case of the following diseases is unusual or unexpected and may have serious public health impact, and thus shall be notified:
  - smallpox, poliomyelitis due to wild-type poliovirus, human influenza caused by a new subtype, severe acute respiratory syndrome (SARS);
* An event involving the following diseases shall always lead to utilization of the notification algorithm, because they have demonstrated the ability to cause serious public health impact and to spread rapidly internationally:
cholera, pneumonic plague, yellow fever, viral hemorrhagic fevers (Ebola, Lassa, Marburg), West Nile fever, other diseases that are of special national or regional concern, e.g. dengue fever, Rift Valley fever, and meningococcal disease.

Any event of potential international public health concern, including those of unknown causes or sources and those involving other events or diseases than listed above shall lead to utilization of the notification algorithm.

1.2.7 Disease registries

Registry is a collection of information about individuals, usually focused on specific diagnosis or condition. Many registries collect information about people who have a specific disease, while others seek participants of varying health status who may be willing to participate in research about a particular disease.

Registries can provide health care professionals and researchers with first-hand information about people with certain conditions, both individually and as a group, and over time, to increase our understanding of that condition. Some registries collect information that can be used to track trends about the number of people with diseases, treatments, etc. Other registries invite people to sign up to be contacted about participating in clinical research. These ask very basic questions about health history that would help determine whether someone is possibly eligible to join a research study.

Disease registry is an organization for the systematic collection, storage, analysis, interpretation and reporting of data on subjects with specific disease or condition.

McGraw-Hill Concise Dictionary of Modern Medicine defines disease registry as a surveillance system that collects and maintains structured records on the new cases of a specific disease or condition for a specified time period and population. A disease registry analyzes, and interprets data those with a common illness or adverse health condition.

Registries provide valuable characteristics concerning the occurrence and risk factors of epidemiologically important diseases. Well established are e.g. cancer registries. There are two main types of registries: hospital-based and population based ones:

Hospital-based registries are concerned with the recording of information on patients seen in a particular hospital. The main purpose being to contribute to patient care by providing readily accessible information on the subjects with the disease, the treatment they received and its result. The data are used mainly for administrative purposes and for reviewing clinical performance. These registries cannot provide measures of the occurrence of the disease in a defined population as not possible to define the populations from which all the cases arise.

Population-based registries seek to collect data on all new cases of a disease occurring in a well-defined population. Usually, the population is that which is resident in a particular geographical region. As a result, the main objective of this type of registry is to produce statistics on the occurrence of the specific disease in a defined population and to provide a framework for assessing and controlling its impact on the community. The emphasis is on epidemiology and public health.

National Health Registries of the Slovak Republic (SR) administered by National Health Information Centre (NHIC), are health information systems, the primary role of which is to collect, process and analyze data on newly diagnosed diseases occurring on a large-scale or those which are socially significant in the population of the SR for the given year - incidence. The total numbers of surviving individuals with diseases monitored in the registries represent prevalence data within a time line. Collection, processing and analysis of these data are important in the field of taking measures in health, economic as well as social area.
List of national health registries of the SR involves: National Cancer Registry, National Diabetes Mellitus Registry, National Congenital Disease Registry, National Cardiovascular Registry, National Registry of Chronic Pulmonary Disease, National Tuberculosis Registry, National Arthroplasty Registry as well as National Registry (NR) of Neurological Disorders, NR of Patients with Inflammatory Rheumatic Disease, NR of Persons with Injury Requiring Inpatient Healthcare, NR of Persons Suspected of Being Neglected, Abused and on Victims of Violence, NR of Electronic Health Records.

National Health Administrative Registries of the Slovak Republic, administered by NHIC, are health information systems that contain data on health care providers and health care workers (National Registry of Health Care Providers, National Registry of Health Workers). The purpose of data collection and their processing within these registries is mainly: database management, fulfilment of identification, registration, integration, information and statistical function of registries at both national and international level, creation and evaluation of statistical outputs, issue of electronic health professional cards.

1.2.8 Standardization

Standard is defined as a comparative tool in environment of information and communication technologies, setting fundamental elements, structure, and formats of data interfaces, quality, time frame and mode of management. The announcement also establishes the course of editing standards, their upgrade, and cancelation.

Disease can be measured in one population or compared between populations. Within one population, it is common to summarize disease burden with the number of cases. Another measure is the crude rate (i.e., $x$ cases / $y$ population at-risk), which is also recognized as the cumulative rate. If the distribution of a modifier of disease frequency (such as age) is different between two populations, a comparison of the crude rates in the two populations can mask the rate. If the goal is to compare rates between populations, it is helpful to standardize the rates, which removes the effect of a potential confounder, such as the age distribution, that differs between the populations.

Standardization is used if the goal is to compare rates between populations, as it removes the effect of a potential confounder, such as the age distribution, that differs between the populations. Standardization is also helpful when comparing rates of one population over time, such as monitoring a disease in a population over many years.

A standardized rate is a measure of disease frequency that facilitates comparisons of populations with a different distribution of one or more potential confounding variables. (e.g. $x$ cases / $y$ population at-risk, adjusted to remove the effect of potential confounder e.g., age).

There are two approaches to standardizing a rate: direct and indirect standardization.

Direct method of standardization: The specific rates in a study population are averaged, using as weights the distribution of a specified standard population. The directly standardized rate represents what the crude rate would have been in the study population if that population had the same distribution as the standard population (a population used as the reference in standardisation) with respect to the variable(s) for which the adjustment or standardization was carried out.

Indirect method of standardization: This method is used to compare study populations for which the specific rates are either statistically unstable or unknown. The specific rates in the standard population are averaged, using as weights the distribution of the study population. The ratio of the crude rate for the study population to the weighted average so obtained is the standardized mortality (or morbidity) ratio, or SMR. The indirectly standardized rate itself is the product (multiple) of the SMR and the crude rate for the standard population, but this product is rarely used in studies.
### Direct standardization – example of calculation

<table>
<thead>
<tr>
<th>Age</th>
<th>Male population</th>
<th>Cases</th>
<th>Incidence rate/100 000</th>
<th>Male population</th>
<th>Cases</th>
<th>Incidence rate/100 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1 900 000</td>
<td>1 406</td>
<td>74.0</td>
<td>26 000</td>
<td>21</td>
<td>80.0</td>
</tr>
<tr>
<td>5-14</td>
<td>3 100 000</td>
<td>186</td>
<td>6.0</td>
<td>30 000</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>15-44</td>
<td>9 400 000</td>
<td>1 786</td>
<td>19.0</td>
<td>127 000</td>
<td>27</td>
<td>21.3</td>
</tr>
<tr>
<td>45-64</td>
<td>4 900 000</td>
<td>7 350</td>
<td>150.0</td>
<td>25 000</td>
<td>42</td>
<td>168.0</td>
</tr>
<tr>
<td>65+</td>
<td>2 000 000</td>
<td>17 400</td>
<td>870.0</td>
<td>5 000</td>
<td>48</td>
<td>960.0</td>
</tr>
<tr>
<td>Total</td>
<td>21 300 000</td>
<td>28 128</td>
<td>132.1</td>
<td>213 000</td>
<td>140</td>
<td>65.7</td>
</tr>
</tbody>
</table>

Appropriate standard in the given example might be the population of males for England and Wales.

### Direct standardization – example of calculation cont.

<table>
<thead>
<tr>
<th>Age</th>
<th>Standard population</th>
<th>Rate for immigrants /100 000</th>
<th>Expected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1 900 000</td>
<td>80.0</td>
<td>1 900 000 x 80.0/100 000 = 1 535</td>
</tr>
<tr>
<td>5-14</td>
<td>3 100 000</td>
<td>6.7</td>
<td>3 100 000 x 6.7/100 000 = 208</td>
</tr>
<tr>
<td>15-44</td>
<td>9 400 000</td>
<td>21.3</td>
<td>9 400 000 x 21.3/100 000 = 2 002</td>
</tr>
<tr>
<td>45-64</td>
<td>4 900 000</td>
<td>168.0</td>
<td>4 900 000 x 168.0/100 000 = 8 232</td>
</tr>
<tr>
<td>65+</td>
<td>2 000 000</td>
<td>960.0</td>
<td>2 000 000 x 960.0/100 000 = 19 200</td>
</tr>
<tr>
<td>Total</td>
<td>21 300 000</td>
<td></td>
<td>31 177</td>
</tr>
</tbody>
</table>

The expected cases are obtained by multiplying the standard population at each age by the age specific rates of the index (immigrant) population. The total of expected cases is 1535 + 208 + 2002 + 8232 + 19 200 = 31 177. The standardized incidence rate for index population of immigrants is: 31 177: 21 300 000 x 100 000 = 146.4 per 100 000

Appropriate standard in the given example might be the incidence rate of the male population for England and Wales.

### Indirect standardization – example of calculation

<table>
<thead>
<tr>
<th>Age</th>
<th>Male population</th>
<th>Cases</th>
<th>Incidence rate/100 000</th>
<th>Male population</th>
<th>Cases</th>
<th>Incidence rate/100 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1 900 000</td>
<td>1 406</td>
<td>74.0</td>
<td>26 000</td>
<td>21</td>
<td>80.0</td>
</tr>
<tr>
<td>5-14</td>
<td>3 100 000</td>
<td>186</td>
<td>6.0</td>
<td>30 000</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>15-44</td>
<td>9 400 000</td>
<td>1 786</td>
<td>19.0</td>
<td>127 000</td>
<td>27</td>
<td>21.3</td>
</tr>
<tr>
<td>45-64</td>
<td>4 900 000</td>
<td>7 350</td>
<td>150.0</td>
<td>25 000</td>
<td>42</td>
<td>168.0</td>
</tr>
<tr>
<td>65+</td>
<td>2 000 000</td>
<td>17 400</td>
<td>870.0</td>
<td>5 000</td>
<td>48</td>
<td>960.0</td>
</tr>
<tr>
<td>Total</td>
<td>21 300 000</td>
<td>28 128</td>
<td>132.1</td>
<td>213 000</td>
<td>140</td>
<td>65.7</td>
</tr>
</tbody>
</table>

Indirect standardization – example of calculation
Indirect standardization – example of calculation cont.

<table>
<thead>
<tr>
<th>Age</th>
<th>Standard Rate</th>
<th>Immigrant Population</th>
<th>Expected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 4</td>
<td>74.0</td>
<td>26 000</td>
<td>74.0 x 26 000 / 100 000 = 19.2</td>
</tr>
<tr>
<td>5 - 14</td>
<td>6.0</td>
<td>30 000</td>
<td>6.0 x 30 000 / 100 000 = 1.8</td>
</tr>
<tr>
<td>15-44</td>
<td>19.0</td>
<td>127 000</td>
<td>19.0 x 127 000 / 100 000 = 24.1</td>
</tr>
<tr>
<td>45-64</td>
<td>150.0</td>
<td>25 000</td>
<td>150.0 x 25 000 / 100 000 = 37.5</td>
</tr>
<tr>
<td>65+</td>
<td>870.0</td>
<td>5 000</td>
<td>870.0 x 5 000 / 100 000 = 43.5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>126.1</td>
</tr>
</tbody>
</table>

The **expected cases** are obtained by multiplying the **standard age-specific rates by the number of persons in each age group of index population** (the immigrants).

The **total expected cases** is 19.2 + 1.8 + 24.1 + 37.5 + 43.5 = 126.1

The standardized incidence ratio – **SIR** (in the case of mortality standardized mortality ratio – **SMR**) is the ratio of the **total observed cases** to the **total expected cases in the index population** (immigrants)

140: 126.1 = 1.11 or 140: 126.1 x 100 = 111 %

The **standardized rate for the index population** (immigrants) is obtained by multiplying the SIR or SMR by the crude rate of the standard population

The **indirectly standardized incidence rate** for index population (immigrants) is 132.1 x 1.11 = 146.5 per 100 000 population.

An international standard population. The idea of an international standard was first suggested by Ogle in 1892, who proposed standard based on the experience of seven European countries. Since then other standards have been proposed without being widely adopted. At a May 1965 subcommittee meeting of the International Union Against Cancer (IUAC) Conference in London three standard populations were suggested, each appropriate for particular population types. One with a high proportion of young people was considered appropriate for comparisons with populations in Africa, the second “European” standard was based on the experience of Scandinavian populations, containing a relatively high proportion of old people and judged suitable for comparison within Western Europe. The third was proposed by Segi in 1960 as an intermediate “world” standard based on the experience of 46 countries. The “European” and “world” standards were subsequently adopted by WHO mainly for calculating age-standardized death rates and are widely used for purposes of direct standardization in practice. These standards are shown in a following table (tab. 2) together with the newly proposed WHO World Standard (shown in abbreviated form) reflecting rise of life expectancy also in populations of developing countries.

<table>
<thead>
<tr>
<th>Age group</th>
<th>World (Segi) standard</th>
<th>European (Scandinavian) standard</th>
<th>WHO World Standard*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>12.00</td>
<td>8.00</td>
<td>8.86</td>
</tr>
<tr>
<td>5-9</td>
<td>10.00</td>
<td>7.00</td>
<td>8.69</td>
</tr>
<tr>
<td>10-14</td>
<td>9.00</td>
<td>7.00</td>
<td>8.60</td>
</tr>
<tr>
<td>15-19</td>
<td>9.00</td>
<td>7.00</td>
<td>8.47</td>
</tr>
<tr>
<td>20-24</td>
<td>8.00</td>
<td>7.00</td>
<td>8.22</td>
</tr>
<tr>
<td>25-29</td>
<td>8.00</td>
<td>7.00</td>
<td>7.93</td>
</tr>
<tr>
<td>30-34</td>
<td>6.00</td>
<td>7.00</td>
<td>7.61</td>
</tr>
<tr>
<td>35-39</td>
<td>6.00</td>
<td>7.00</td>
<td>7.15</td>
</tr>
<tr>
<td>Age group</td>
<td>World (Segi) standard</td>
<td>European (Scandinavian) standard</td>
<td>WHO World Standard*</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------</td>
<td>---------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>40-44</td>
<td>6.00</td>
<td>7.00</td>
<td>6.59</td>
</tr>
<tr>
<td>45-49</td>
<td>6.00</td>
<td>7.00</td>
<td>6.04</td>
</tr>
<tr>
<td>50-54</td>
<td>5.00</td>
<td>7.00</td>
<td>5.37</td>
</tr>
<tr>
<td>55-59</td>
<td>4.00</td>
<td>6.00</td>
<td>4.55</td>
</tr>
<tr>
<td>60-64</td>
<td>4.00</td>
<td>5.00</td>
<td>3.72</td>
</tr>
<tr>
<td>65-69</td>
<td>3.00</td>
<td>4.00</td>
<td>2.96</td>
</tr>
<tr>
<td>70-74</td>
<td>2.00</td>
<td>3.00</td>
<td>2.21</td>
</tr>
<tr>
<td>75-79</td>
<td>1.00</td>
<td>2.00</td>
<td>1.52</td>
</tr>
<tr>
<td>80-84</td>
<td>0.50</td>
<td>1.00</td>
<td>0.91</td>
</tr>
<tr>
<td>85+</td>
<td>0.50</td>
<td>1.00</td>
<td>0.63</td>
</tr>
<tr>
<td>Total</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

* For purposes of comparison, the WHO Standard age group 85+ is an aggregate of the age groups 85-89, 90-94, 95-99

1.2.9 Descriptive epidemiological studies

Data on diseases and with health related states and problems in a society (e.g. population of a country) or in a part of it (e.g. in an age group) are frequently obtained in descriptive epidemiologic studies. They document the state of health of populations being concerned with and designed to describe exactly the existing distributions of variables. Descriptive studies describe patterns of disease occurrence in relation to variables such as persons, place and time.

**With respect to the time**, cross-sectional (prevalence) studies and longitudinal (cohort) studies can be distinguished.

**Cross-sectional (prevalence) studies** are used to find out occurrence of a variable in a certain point of time.

For example if at a certain point of time the frequency of HBsAg positivity is determined in a randomly selected sample from a population of interest, it is a descriptive cross-sectional study. As prevalence of the HBsAg was examined, it is referred to also as a study.

**Longitudinal (cohort) descriptive studies** are used to follow and describe the occurrence of diseases and health related states during a selected time interval. There can be followed e.g. an incidence and mortality rates of specific illness during years in a cohort (cohort is a group of individuals with set personal characteristics) in which specified variables are followed for a long time period.

For example one year follow-up of individuals found HBsAg positive can show whether carrier state turned to chronicity.

According to their priority target orientation, descriptive studies are being also divided in to two major groups, those that primarily deal with individuals and those that relate to populations.

Among studies dealing with individuals being categorized the case reports, case-series reports, as well as cross-sectional descriptive studies and surveillance type of studies. Surveillance being classified as an independent epidemiologic method and is presented separately.

**Case reports** is a detailed description of disease occurrence in a single person. Unusual features of the case may suggest a new hypothesis about the causes or mechanisms of disease.
E.g. In April 1983 it had not yet been shown that AIDS could be transmitted by blood or blood products. An infant born with Rh incompatibility required blood products from 18 donors over 8 weeks and subsequently developed unusual recurrent infections with opportunistic Candida agents. The infant’s T cell count was low, suggesting AIDS. There was no family history of immunodeficiency, but one of the blood donors was found to have died of AIDS. This led the investigators to hypothesize that AIDS could be transmitted by blood transfusion.

Case series is a report on the characteristics of a group of subjects who all have a particular disease or condition. Common features among the group may suggest hypotheses about disease causation. The “series” may be small or it may be large (hundreds or thousands of “cases”). The chief limitation is that there is no comparison group.

Cross-sectional surveys assess the prevalence of disease and the prevalence of risk factors at the same point in time and provide a “snapshot” of diseases and risk factors simultaneously in a defined population.

For example, periodical surveys, asking about health status and risk factors and behaviors at that point in time in random samples of the US population as in the Health Interview Survey (HIS), and the National Health and Nutrition Examination Survey (NHANES). Ecological (correlational) studies can be categorized among studies related to population, as the unit of observation is an entire population or group.

These studies examine the correlation between the average exposure in various populations with the overall frequency of disease within the populations.

In studies on lifestyle factors, investigators use commerce data to compute the overall food consumption by various nations. Then they calculate the average (per capita) consumption per person by dividing total national consumption by the number of people in a given country. In reality, food consumption varies widely within nations, and the calculated exposure is an average assuming that everyone ate the average amount the food. This average exposure is then correlated with the overall disease frequency in each country.

Advantages: the data required in ecological studies is frequently readily available. Commerce data can be used to estimate a population’s total consumption of products (possible risk factors) such as meat, tobacco, fish, etc. So, these studies are quick and inexpensive.

The correlation coefficient or an r value provides a measure of how closely the observed data points conform to a straight line. The slope of the line would be a measure of the strength of association. The value of a correlation coefficient is from +1 (a perfect positive correlation) and −1 (a perfect negative correlation).

Limitations: the exposure is the average exposure for an entire population or group. Since there is no information about the risk factor status or the outcome status of individual people, we cannot directly link the risk factor to the disease.

Example: a correlational study suggests that the frequency of colon cancer increases as meat consumption increases – but it is not clear that the people who ate the most meat were the ones who got colon cancer.

Common features in descriptive studies may suggest hypotheses but these need to be tested with some sort of analytical study before an association can be accepted as valid.

1.2.10 Data presentation

In order to be useful, the data must be organized and analyzed in a thoughtful, well structured way, and the results must be communicated clearly and effectively to the health professionals and the community at large. Some simple standards are useful
to promote clear presentation. Compiled data are commonly summarized in tables, graphs or figures, or some combinations.

Tables are the best way to show exact numerical values. They are preferable for many small data sets and work well when data presentation requires many localized comparisons.

Simple guidelines suggested for preparing tables involve:
- providing a concise descriptive title,
- labelling the rows and columns,
- providing the units in the column headers,
- providing the column total, if appropriate,
- providing an additional explanatory information in a footnoted legend

For example, table showing frequency of treatment of high blood pressure

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of treated /total number</th>
<th>Relative frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>611 / 1 622</td>
<td>37.7</td>
</tr>
<tr>
<td>Female</td>
<td>608 / 1 910</td>
<td>31.8</td>
</tr>
<tr>
<td>Total</td>
<td>1 219 / 3 532</td>
<td>34.5</td>
</tr>
</tbody>
</table>

Simple guidelines for preparing figures are as follows:
- title of the figure must be concise and descriptive,
- the vertical and horizontal axes must be clearly labeled showing units where appropriate,
- appropriate scales must be used for the axes that display the results without exaggerating them with ranges that are either too expansive or too restrictive,
- for line graphs with multiple groups a simple legend can be included if needed.

Relative frequency of antihypertensive medication use in men and women

![Graph showing male and female relative frequency of antihypertensive medication use](image_url)

Statistical analysis of the focus of infection

During work in an outbreak area, attention should be paid to several problems relevant from epidemiological aspects. The most important problems to be solved are:
- identification of source or sources of infection,
- route or routes of infection transmission,
- number of persons potentially infected.

In solving these problems, the following statistical methods may be useful:
- Time charts – showing the frequency of cases in time – with the y axis representing the number of cases and the x axis representing the time periods. The situation in the focus of infection is plotted as a curve (or as columns), expressing the number of
cases in each time period – so-called epidemic curve. The shape of the epidemic curve can provide clues about the nature of the epidemic outbreak. The pattern of the time sequence of the cases depends on the mode of transmission of infection – for example a steeply rising curve with a sharp peak indicates explosive epidemics, characteristic of some water-borne or food-borne intestinal infections.

Linear prevalence diagram – showing e.g. in each case the duration from onset of disease to isolation, length of isolation, etc. This diagram allows to calculate the number of non-isolated cases, hospitalized cases, isolated cases, etc. in each time point. Similarly cumulation diagram shows the number of cases in each time point.

Epidemic maps (spot maps) – are usually intended to illustrate the distribution in space of patients affected, so that any associations, e.g. with food or water supplies, can be readily appreciated.

Indices of the quality of epidemic measures are usually expressed by average time periods:
- from the first symptoms of a disease to addressing health care (index of health awareness of people),
- from the visit of a physician to specifying a clinical diagnosis (index of diagnostic skills of physicians),
- from delivery of material to the laboratory to specifying a laboratory diagnosis (index of diagnostic skills of a laboratory),
- from specifying the diagnosis to isolation, hospitalization, disinfection in a focus of infection, etc. (index of quality of preventive and repressive measures).

References:
http://www.healthknowledge.org.uk/e-learning/epidemiology/specialists/standardisation
1.3 ANALYTIC EPIDEMIOLOGY

Analytic studies are designed to study determinants of disease, to evaluate associations and to test causal hypotheses. One should however always consider that a single analytic study does not prove causality; it can rather provide suggestive evidence of a causal relationship that requires additional evidence to confirm the causality.

Analytical studies are either longitudinal or cross-sectional. In longitudinal studies (case-control study, cohort study), the time sequence can be inferred between exposure and disease; in other words, exposure precedes disease. In a cross-sectional (transversal) study, exposure and disease information relate to the same time period; in these studies, it may not always be correct to presume that exposure preceded disease.

Reasoning in epidemiology follows usual pattern of consecutive steps. Those are development of a hypothesis, testing of the hypothesis on an exposed population and an appropriate control group, systematic collection and analysis of data to determine whether a statistical association exists, assessment of validity of any observed association by excluding possible alterations such as chance, bias or confounding and finally judgement of possible cause-effect relationship between exposure and disease.

Four basic methods of forming hypotheses are described. The method of difference describes a situation when the frequency of a disease is markedly different in two populations and certain suspected factor influences only one of these populations, so this factor may be the cause of the disease of interest. The principle of the method of agreement is that if a suspected factor is common to two or more different populations associated with the presence of a disease, then this factor may be the cause of the disease. If the frequency of a disease varies with the frequency or strength of some factors (such as increased risk of myocardial infarction MI with increased number of cigarettes smoked), the factor with similar variation may be the cause of the disease (the method of concomitant variations). If the distribution of a disease is similar to that of some other and better known disease, it is possible that certain causes may be common to both diseases. This was revealed by method of analogy.

Causality of an association

Epidemiologic studies report associations between an exposure and an outcome, and such associations may be causal leading to better diagnostics, therapy and finally to prevention. But many associations are not causal. Separating whether an association between exposure and disease is causal or exposure is rather a marker of risk of disease or even that the association is by chance alone critically important for proper interpretation of observed association. Epidemiological data should be interpreted with caution and in the context of other available scientific information.

Epidemiologists use the following recommended criteria to assess the possible causality of associations.

- Biological plausibility. When the association is supported by evidence from clinical research or basic sciences about biological behavior or mechanisms, an inference of causality is strengthened.

- Temporal association. Exposure should precede the disease by a period of time consistent with a proposed biological mechanism, and in most epidemiological studies this can be inferred.

- Study precision and validity. Individual studies that provide evidence of an association are properly designed with an adequate number of study participants (precision) and well conducted with valid results (i.e., the association is not likely due to systematic bias).
• **Strength of association between exposure and disease.** The greater the magnitude of the risk (or benefit) i.e. measured by relative risk or odds ratio (see later), the less likely the association is to be spurious or due to some unsuspected or uncontrolled confounding. However, a causal association cannot be ruled out simply because a weak association is observed. There are not strictly reliable criteria to confirm casual association between cause/risk factor and sequel, conclusions about association are often preliminary.

*Metanalysis* is a methodological approach using statistical methods for compilation of results of published epidemiological studies dealing with the same problem. Randomized clinical intervention studies being without systematic errors (bias) and confounding factors are preferably used for this purpose. The result from metaanalysis of several studies is more relevant then the results from all single studies included in the analysis.

• **Consistency.** Similar results are reported from other studies performed under similar conditions (metaanalysis). Repeated observation of an association under different study conditions supports an inference of causality, but its absence does not rule out causality. This is similar to the replication of results in laboratory experiments.

• **Specificity.** A putative cause or exposure leads to a specific effect or disease. The presence of specificity argues for causality, but its absence should not rule it out.

• **Dose–response relationship.** The observation of a gradient of risk associated with the degree of exposure leading to adequate changes of disease occurrence in the same manner makes a causal interpretation more plausible.

• **Reversibility.** An observed association could lead to some preventive action, when removal or reduction of the exposure leads to a reduction of disease or risk of disease.

These criteria are useful but they do not reflect the complexity and interaction of the various risk factors involved in many chronic disease and they do not give an absolute proof of causation.

In epidemiology, we can see that mainly analytic studies rarely, if ever, study entire populations. Studies are usually performed on a *sample population*. However research studies would like to infer results from a particular study sample to the whole population.

Analytical studies are used to *test specific hypotheses* - to study determinants of disease, to evaluate associations and to test causal hypotheses. Errors that occur during the design and conduct of a study can lead to a false or spurious association or a measure of risk that departs systematically from the true value. In general, study results can be explained by one of the four conditions:

1. The observed result is due to random error (chance)
2. The observed result is due to systematic error (bias)
3. The observed result is due to confounding
4. The observed result is valid

All studies and observed associations require evaluation of random and systematic error so that results can be interpreted properly.

**Random error (chance)**

Random error is when a value of the sample measurement diverges – due to chance alone – from that of the true population value. Random error causes inaccurate measures of association. There are three major sources of random error:

• individual biological variation;
• sampling error; and
• measurement error.
Chance can never be eliminated entirely, but it can be minimised by proper methodology. Sample size and representativeness of a sample are of crucial importance. Usually a small sample is not representative of all the population's variables. Individual variation always occurs (e.g. due to diurnal variation, age, diet, exercise...) and no measurement is perfectly accurate (accuracy and precision are important). The best way to reduce sampling error is to increase the size of the study. When larger samples are selected, the samples will more closely mirror the characteristics of the population in question.

The likelihood that an observed association is due to random error is assessed by the level of statistical significance ("p" value) or the confidence interval (C.I.).

**Level of significance** quantifies the degree to which chance variability may account for the observed results. **P-value** relates to probability that an effect at least as extreme as that observed in a particular study could have occurred by chance alone, given that there is truly no relationship between the exposure and disease. P < 0.05 means that the probability of this result happening by chance is less than 5% (1 in 20 chance). By convention, if \( p < 0.05 \) then we consider the association between the exposure and disease to be statistically significant. The 5% level chosen is equivalent to calculating a 95% confidence interval for a relative risk or odd ratio.

The **confidence interval** (CI) is the range within which the true magnitude of effect lies with a certain degree of assurance. If a particular experiment is conducted an infinite number of times, with each experiment having a fixed sample size, then some interval can be placed around each sample mean such that 95% of all the intervals contain the true population mean. For odds ratios and relative risks, **if the confidence interval includes 1.0, it is assumed that there is no statistically significant difference** between the two groups. The choice of 95% is arbitrary, but is very commonly used. For example, a relative risk of 1.9 (95% CI 0.6, 3.1) means that we are 95% confident that the true relative risk is in the range 0.6 to 3.1. However, because this range includes 1.0, the association is not statistically significant, as RR = 1 means no association. The narrower the confidence interval, the less variability was present and usually it reflects also large sample size. The wider CI, the greater the variability in the estimate of effect and frequently reflecting a smaller sample size.

In conclusion a small P value (p < 0.05 – the lower, the better) or a CI that does not include unity (1.0) suggests that the difference observed is statistically significant and that chance may be an unlikely explanation for an observed association. On the other hand the association still may, nevertheless, be spurious because of systematic error.

**Systematic error (bias)**

Bias occurs when results differ in a systematic manner from the true values. A study with a small systematic error is said to have a high accuracy. Accuracy is not affected by sample size. There are reported more than 30 systematic errors.

**The possible sources of systematic error in epidemiology are:**

- **Selection bias** occurs when noncomparable criteria are used to enrol subjects in a study.
- **Measurement (misclassification) bias** occurs when the individual measurements or classifications of disease or exposure are inaccurate and lead to the misclassification of either disease or exposure, or both. There are many sources of measurement bias – e.g. recall bias, observer bias.
- **Recall bias** can occur when there is a differential recall of information by cases and controls; for instance, cases may be more likely to recall past exposure, especially if it is widely known to be associated with the disease under study. Recall bias is of particular concern in case-control studies.
- **Observer bias** can result when investigator knows the exposure status (or disease status); this knowledge can influence measurements and interpretation of data.
Confounding

A confounder is a variable that is causally related to the disease of interest and is also associated with the exposure under study in the study population, but is not a consequence of this exposure. A problem arises if the confounder (itself a determinant or risk factor for the disease) is unequally distributed between the exposure subgroups. It may thus create the appearance of a cause-effect relationship that does not actually exist.

A typical example of confounding is observation of association between coffee consumption and increased risk of myocardial infarction (MI) due to smoking effect. But it is known that there is higher presence of smokers among coffee drinkers and after controlling for smoking status the association between coffee drinking and risk of MI disappears.

Confounding can be controlled, either through study design or during the analysis of results. Approaches commonly used to control confounding in the design a study are restriction of the study population (e.g. only non-smokers), matching (for potential confounder) and randomisation of exposure (ideally useful in experimental studies). In analysis of study confounding can be controlled by stratification and multivariate analysis.

1.3.1 Cross-sectional studies

A cross-sectional study refers to a study design in which ascertainment of the exposure and the outcome (disease) occurs simultaneously. It includes as subjects all persons in the population at the time of ascertainment or a representative sample of all such persons, including those who have the disease, and has an objective limited to describing the population at that time. Cross-sectional study measures the prevalence of disease and thus is often called prevalence study. In addition, it seeks associations, generates and tests hypotheses and, by repetition in different time periods, can be used to measure changes.

In this type of study status of an individual with respect to the presence or absence of both exposure and disease is assessed at the same point in time or over a short period of time. Subjects of cross-sectional studies are however selected irrespective of the presence or absence of the characteristics of interest for hypothesis testing (regardless of exposure or disease status). Cross-sectional surveys are sometimes thought to provide a ‘snapshot’ of health.

In practice, cross-sectional studies can include an element of both descriptive and analytic types of design depending on whether the prime purpose is to provide descriptive estimates of the population's parameters or to test hypotheses about the relationships between exposure (risk factor, etiology) and disease.

One of the most common cross-sectional analytical studies is the survey, in which a random sample is drawn to give an accurate representation of the population. It is similar to a descriptive survey except that the purpose of the analysis is to record associations between variables, rather than merely to report frequencies of their occurrence. Data from repeated cross-sectional surveys using independent random samples with standardized definitions and survey methods provide useful indications of trends. Many countries conduct regular cross-sectional surveys on representative samples of their populations to assess the health care needs of populations.

An important disadvantage of cross-sectional studies is the inability to discern a temporal relationship between the exposure and the outcome because measurement of exposure and disease are made at the same point of time. It in fact gives no indication of the sequence of events; therefore it may be impossible to determine which came first. This study thus cannot provide support for an inference of causation.
**Strengths of cross-sectional studies:**

- Relatively easy and inexpensive to conduct and tend to be carried out over a relatively short time period;
- Often based on a sample of the general population and therefore can estimate prevalence of outcome of interest;
- Many outcomes and risk factors can be assessed;
- Useful for public health planning, understanding disease etiology and for the generation of hypotheses;
- Can be utilized as cohorts in the future;

**Limitations of cross-sectional studies:**

- Difficult to separate cause and effect and make causal inference;
- Only a snapshot: the situation may provide differing results if another timeframe had been chosen;
- Prevalence-incidence bias (also called Neyman bias). A series of prevalent cases will have a higher proportion of cases with disease of long duration than a series of incident cases. In the case of longer-lasting diseases, any risk factor that results in death will be under-represented among those with the disease.
- Possible false classification of disease status in a person in remission or under effective treatment, if periods of exacerbations and remissions occurs

As an example of a cross-sectional study, we can use a paper of Selhub J. et al, 1995 that tested hypotheses concerning the association between homocysteine concentration and carotid artery atherosclerosis.

**Association between Plasma Homocysteine Concentrations and Extracranial Carotid-Artery Stenosis**

**Background**

Epidemiologic studies have identified hyperhomocysteinemia as a possible risk factor for atherosclerosis. The aim of the study was to determine the risk of carotid-artery atherosclerosis in relation to both plasma homocysteine concentrations and nutritional determinants of hyperhomocysteinemia.

**Methods**

Cross-sectional study of 1041 elderly subjects (418 men and 623 women; age range, 67 to 96 years) from the Framingham Heart Study was performed. There was examined the relation between the maximal degree of stenosis of the extracranial carotid arteries (as assessed by ultrasonography) and plasma homocysteine concentrations, as well as plasma concentrations and intakes of vitamins involved in homocysteine metabolism, including folate, vitamin B₁₂, and vitamin B₆. The subjects were classified into two categories according to the findings in the more diseased of the two carotid vessels: stenosis of 0 to 24 percent and stenosis of 25 to 100 percent.

**Results**

The prevalence of carotid stenosis of >25 percent was 43 % in the men and 34 % in the women. The odds ratio for stenosis of >25 percent was 2.0 (95 percent confidence interval, 1.4 to 2.9) for subjects with the highest plasma homocysteine concentrations (>14.4 μmol per litre) as compared with those with the lowest concentrations (<9.1 μmol per litre), after adjustment for sex, age, plasma high-density lipoprotein cholesterol concentration, systolic blood pressure, and smoking status (P<0.001 for trend). Plasma concentrations of folate and pyridoxal-5′-phosphate (the coenzyme form of vitamin B₆) and the level of folate intake were inversely associated with carotid-artery stenosis after adjustment for age, sex, and other risk factors.

**Conclusions**

High plasma homocysteine concentrations and low concentrations of folate and vitamin B₆, through their role in homocysteine metabolism, are associated with an increased risk of extracranial carotid-artery stenosis in the elderly.

How can we interpret these data?

In addition to description of parameters of interest - both prevalence of carotid stenosis (disease) and quartiles of homocysteine concentration (exposure) we can also conclude that there is an association between the two variables – more subjects in upper quartiles of homocysteine suffered of carotid stenosis compare to subjects in lower quartiles. However, we are not able to know from the study whether increased homocysteine level preceded the development of carotid stenosis or the increased level is a consequence of the carotid stenosis, as both parameters were evaluated in the same point of time.

1.3.1 Case-control studies

The key feature of a case-control study is selection of subjects based upon their disease status. In a case-control study people with the disease or risk factor of interest (cases) are compared with people without that disease or risk factor (controls). The proportions of cases and controls that have been exposed to potential risk factors (exposures) are determined and compared. Case-control studies have been called retrospective studies since the investigator is looking backward from the disease to a possible cause.

Case-control studies can reveal temporal relationships between exposure and outcome, strengthening the case for a causal relationship. Temporality in case control studies is demonstrated by assuring that an exposure was present prior to the development of the disease.

This type of study is the most frequently performed type of observational analytic study.
A case-control study starts with a group of cases, then select controls that represent the source population by the exposure status and subsequently it compares the odds of exposure among cases and controls. It is crucial to make sure that the exposure preceded the disease in cases.

Ideally, well defined cases are selected from a clearly defined source population and controls are chosen from the same population that yielded the cases. Optimally, newly diagnosed (incident) cases are included, however often also previously existing (prevalent) cases are involved.

In these circumstances, however, possibility that the exposure may affect the prognosis or the duration of the disease is of concern and prevalent cases can lead to an over-representation of cases with long duration. Moreover, if a study subject had the disease for a long period of time, it could be difficult to distinguish whether exposures preceded the disease or occurred after the disease occurred.

Case-control studies are prone to bias and confounding more than other study designs. Selection bias - that can occur when the inclusion of cases or controls, or both depends in some way on the prior exposure - poses a particular threat to this type of study. It can arise when an inappropriate control group is chosen, preferential diagnosis of exposed cases is done (e.g. after media attention and publicity regarding exposure and disease), or low or unequal participation rates for cases and controls is present. As a consequence the exposure of the cases (or controls) studied differs from that of all cases arising from the source population (or all persons in the source population without the disease). Schematic diagram of the origin of selection bias is described in the figure 3.
Figure 3. Origin of selection bias in a case-control study

Source: modified from Greenberg et al. Medical Epidemiology. 2nd edition, 1996 Appleton& Lange
In cases – exposed persons with disease were more likely than unexposed persons with disease to be selected for the study. In controls – exposed persons were less likely to be selected for study than were unexposed

Also another type of bias – recall bias is together with selection bias of particular concern in case-control studies. This may happen when cases and controls recall exposures differently. For example when diseased subjects are aware in advance of possible association between the disease and the exposure they can think harder and remember the exposure more compare to controls (and thus may over report the exposure). One of possible solutions of this problem can be the use of verification of exposure through other methods – for example through the use of biologic markers. In our example of case-control design plasma homocysteine level is measured as a biologic marker of exposure.

Case-control studies often use matching to increase the degree of similarity between case and control subjects and to make case-control comparison less subject to confounding - the possibility that other factors account for the association between exposure and outcome. Matching is pairing of one or more control subjects to each case on the basis of specified risk factors (other than the risk factor of interest). Age, sex or ethnicities are common factors evaluated in matching, but different factors can be included based on specific disease and exposure of interest.

Matching cases and controls on several characteristics can however create difficulties in finding controls and run the risk of ‘overmatching’. Overmatching leads to missed associations because the causal factors have been inadvertently matched for and can create a selection bias.

In conclusion, in order to minimise bias, care must be taken in the selection of both cases and controls, in establishing definitions of disease, risk factors and in ensuring there are no confounding associations between detection of disease and risk factor exposure.

Case-control studies are particularly suitable to evaluate rare diseases, diseases with long latency periods or as a preliminary study where little is known about the association between the risk factor and disease of interest. A very practical advantage of a case-control study is that the sample size required for this type of study tends to be smaller, can be completed relatively rapidly and inexpensive compared to other analytic de-
signs (e.g. cohort study). Moreover, once the case and control groups are established a researcher can investigate multiple etiologic factors for a single disease.

In our example of the study evaluating plasma homocysteine levels with premature coronary artery disease case and control subjects were also compared with respect to lipids’ levels.

The disadvantages of case-control studies relate particularly to their susceptibility to bias, particularly selection bias and recall bias. Another limitation of case-control studies is that they are inefficient for the evaluation of rare exposures, unless the attributable risk is high. The temporal relationship between exposure and disease may be sometimes difficult to establish, especially when prevalent cases are involved and there is no clear information whether the exposure was present in a subject before the disease onset.

Based on a priori selection of subjects based on presence or absence of disease it is not possible directly compute incidence of disease. An indirect estimate of the risk ratio, however, can be calculated as the odds ratio and 95% confidence interval expressing a measure of association between exposure and disease occurrence. The OR calculated from a case-control study provides a valid estimate of the relative risk when the disease is rare (as is the case for many chronic conditions evaluated in case-control studies).

<table>
<thead>
<tr>
<th>Exposed</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Not exposed</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Odds of exposure</td>
<td>a/c</td>
<td>b/d</td>
</tr>
</tbody>
</table>

\[ \text{OR} = \frac{a \times d}{b \times c} \]

95% Confidence intervals are calculated using the formula shown below

Upper 95% CI = \( e^{\ln(\text{OR}) + 1.96\sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}} \)

Lower 95% CI = \( e^{\ln(\text{OR}) - 1.96\sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}} \)

\( \ln \) - natural logarithm, Euler number \( e = 2.718281828 \)

**Example:** In a hypothetical case-control study association between smoking and myocardial infarction (MI) was evaluated in 100 MI survivors and 200 controls without MI

<table>
<thead>
<tr>
<th>MI Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>30</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>70</td>
</tr>
<tr>
<td>All</td>
<td>100</td>
</tr>
</tbody>
</table>

\[ \text{OR} = 30 \times 165 / 35 \times 70 = 2.02; \text{ 95\% CI: 1.10-3.68} \]

Upper 95% CI = \( e^{\ln(2.02) + 1.96\sqrt{\frac{1}{30} + \frac{1}{35} + \frac{1}{70} + \frac{1}{165}}} \) = 3.68

Lower 95% CI = \( e^{\ln(2.02) - 1.96\sqrt{\frac{1}{30} + \frac{1}{35} + \frac{1}{70} + \frac{1}{165}}} \) = 1.10

The odds ratio for MI in smokers compared to nonsmokers is 2.02 indicating increased odds of MI for smokers. As the 95% CI is 1.10-3.68, we are 95% certain that the
true odds lies between 1.10 and 3.68 and since this interval does not include the value 1.00, the measured OR of 2.02 is statistically significant at the 5% level of significance.

**Strengths of case-control studies:**
- relatively quick and cheap compared to other analytic designs (cohort studies)
- particularly useful to the evaluation of diseases with long latency periods
- optimal for studying rare diseases
- can be repeated
- can examine multiple risk factors for a single disease
- tend to require a smaller number of subjects than other designs

**Limitations of case-control studies:**
- Cannot directly compute incidence rates of disease and relative risk
- Not efficient for the study of rare exposures
- In some situations, the temporal relationship between exposure and disease may be difficult to establish
- Prone to bias, particularly selection and recall bias and confounding
- Provide less accurate results (not relevant information from records, not completed data, not satisfactory memory of certain issues, events, etc.)

As an example of a case-control study, we can use a paper of Genest JJ. et al, 1990 that tested hypotheses concerning the association between plasma homocysteine levels and coronary artery disease.

**Plasma homocyst(e)ine levels in men with premature coronary artery disease.**

Plasma homocyst(e)ine (that is, the sum of free and bound homocysteine and its oxidized forms, homocystine and homocysteine-cysteine mixed disulfide) levels were determined in 170 men (mean age +/- SD, 50 +/- 7 years) with premature coronary artery disease diagnosed at coronary angiography and in 255 control subjects clinically free of coronary artery disease (mean age 49 +/- 6 years). Patients with coronary artery disease had a higher homocyst(e)ine level than control subjects (13.66 +/- 6.44 versus 10.93 +/- 4.92 nmol/ml, p less than 0.001). High density lipoprotein (HDL) cholesterol levels were lower (32 +/- 10 versus 46 +/- 13 mg/dl, p less than 0.001) and triglycerides levels were higher (193 +/- 103 versus 136 +/- 106 mg/dl, p less than 0.001) in the coronary disease group. Plasma total cholesterol and low density lipoprotein (LDL) cholesterol levels were not significantly different between patients with coronary disease and control subjects. The presence of hypertension, smoking or diabetes mellitus did not significantly alter homocyst(e)ine levels in the patient or the control group. Patients who were not taking a beta-adrenergic blocking drug (n = 70) had a nonsignificantly higher homocyst(e)ine level than did patients taking this class of drugs (n = 100) (14.67 +/- 8.92 versus 12.95 +/- 3.77 nmol/ml, p = 0.087). By design, none of the control subjects were taking a beta-blocker. No significant correlations were observed between homocyst(e)ine and age, serum cholesterol, LDL cholesterol, HDL cholesterol or triglyceride levels. It is concluded that an elevated plasma homocyst(e)ine level is an independent risk factor for the development of premature coronary atherosclerosis in men. (Genest JJ et al. *J Am Coll Cardiol* 1990; 16:1114-1119)

In general new problem started to be studied by case-control study and in the case of positive results, these are then verified in cohort studies.

**1.3.3 Cohort studies**

Cohort is often used to designate a group of people who share a common experience or condition. Cohort study is the term that is typically used to describe an epidemiologic investigation that follows groups with common characteristics. An important feature of cohort studies is that outcome (disease) of subjects included into studies is unknown
at the beginning of the study and investigators observe exposure status, which occurs “naturally” (the exposure is not assigned to the study participants as it is in clinical trials).

A cohort study typically starts with a group of individuals who are \textit{free of disease} of interest; it collects information on exposure and divides individuals into exposed and unexposed. Then it \textit{follows the exposed and the unexposed people over time} in order to determine the \textit{incidence} of symptoms, disease, or death (outcome or disease). The numbers of newly occurring (incident) cases of disease (or other outcome) are recorded and compared between the groups with and without exposure. Cohort studies are also known as \textit{longitudinal, incidence or follow-up studies}.

Cohort studies can be divided according to timing of measurements to prospective and retrospective (Figures 4, 5)

\textit{Figure 4. Schema of a prospective cohort study}

Usually, a cohort study is \textit{prospective} (Fig. 4), where participants are grouped on the basis of past or current exposure and are followed into the future in order to observe the outcomes of interest. \textit{Prospective cohort study} design is more commonly used because data collected in a prospective cohort study are usually more complete and accurate compare to retrospective one.

Occasionally, a cohort study is \textit{retrospective} (or historical). It proceeds forward in time according to the principles of a cohort study; however the data on prior exposure and disease are collected retrospectively. So both the exposures and outcomes have already occurred prior to the beginning of the retrospective cohort study (Figure 5). The advantage of the retrospective cohort design over prospective design is that retrospective study can be done more rapidly and with lower cost. On the other hand, information on past exposure and disease must be available and one must rely upon such information. This may result in less complete and accurate information than data collected in a prospective study.
It is sometimes possible to insert a case-control study to a cohort study. The new cases of disease identified are incident cases and controls (matched to important parameters such as age and sex with cases) can also be identified from within the cohort. This is known as a nested case-control study. The nested case-control design makes cohort studies less expensive as the cases and controls both come from a defined cohort, for which some information on exposures and risk factors is already available.

Once a cohort is established, investigators are free to study more than one outcome, provided that the study subjects are free of each outcome of interest when the study begins. For example if smoking is an exposure and myocardial infarction is a disease of interest, once smokers and non-smokers are identified, investigators could study whether smoking is associated not only with myocardial infarction but also with the development of lung cancer, provided they exclude individuals who have evidence of lung cancer at the beginning of the study.

A well designed cohort study is particularly efficient for study of rare exposures or risk factors, because this type of study allow also selective inclusion of exposed persons.

In general, potential for selection bias is less of concern in cohort studies, however accuracy of classification of both exposure and disease status is crucial in avoiding possible sources of bias.

Unlike cross-sectional studies, cohort studies can elucidate temporal relationships between exposure and disease, and thus strengthens evidence for the exposure to be a possible cause of the disease. Cohort studies provide the best information from observational analytic studies about the causation of disease and allow direct measurement of incidence of disease in the exposed and nonexposed groups.

Confounding is a major limitation of observational studies. Also cohort studies are therefore subject to possibility that other factors that are linked with the exposure of interest could account for some or all of the associations that are observed. Classical example of confounding is an association of coffee drinking with myocardial infarction. However, it is believed that smoking is a confounder because it is associated with both coffee drinking and with myocardial infarction. Smoking status is most likely confounding the relationship between coffee drinking and myocardial infarction, making it appears there is a relationship when in fact there is none.
Cohort studies may be inefficient for the evaluation of rare diseases or if the disease has a long latency period. If the disease under study is rare, it may require so large a sample size that it would be impractical and expensive to complete such a study. Even when more common disease is evaluated, cohort study often takes a long time to complete and is expensive, especially if prospective.

Subjects in cohort studies are often followed-up for a long period of time which can lead to various problems. Validity of the results can be seriously affected by losses to follow-up – subjects may move away or die from other causes than the disease of interest. With large number of lost subjects or when the lost subjects differ in outcome from those who remained in the study, the validity of the results can be affected seriously. Exposure status may also change during the follow-up.

Comparison of the occurrence of symptoms, disease, and death in the exposed and unexposed groups is the main objective of the analysis of cohort study. The occurrence of the outcome is usually measured using incidence (cumulative incidence or incidence rates), and the relationship between the exposure and disease is quantified using absolute or relative difference between the risks or rates. Two groups (cohorts of exposed and nonexposed) are usually compared, but cohort studies can involve also more groups (e.g. normal weight, overweight, obese). Once the incidence of disease in each group is determined one can compare these incidences – most commonly calculating relative risk and attributable risk. The relative risk (RR) is ratio of the incidence of disease in subjects with a risk factor or exposure ($I_e$) to the incidence of disease in subjects without a risk factor -unexposed ($I_{ne}$). Attributable risk (AR) (or risk difference) is the difference between the incidence (proportion or rate) in the exposed and nonexposed groups ($I_e - I_{ne}$) and it describes excess or additional disease due to the exposure.

In a study with multiple groups a reference group must be selected (e.g. normal weight) and then one can calculate a relative risk for each exposed group (e.g. overweight, obese) in relation to the reference group.

$$\begin{array}{|c|c|c|}
\hline
\text{Disease} & \text{No disease} \\
\hline
\text{Exposed} & a & b & I_e = \frac{a}{a+b} \\
\text{Not exposed} & c & d & I_{ne} = \frac{c}{c+d} \\
\hline
\end{array}$$

$$RR = \frac{I_e}{I_{ne}} = \frac{a/a+b}{c/c+d}$$

95% Confidence intervals are calculated using the formula shown below

Upper 95% CI = $e^{\ln(RR) + 1.96\sqrt{(1/a - 1/(a+b) + 1/c - 1/(c+d))}}$

Lower 95% CI = $e^{\ln (RR) - 1.96\sqrt{(1/a - 1/(a+b) + 1/c - 1/(c+d))}}$

$$AR = I_e \cdot I_{ne}$$

**Example:** In a hypothetical cohort study association between smoking and myocardial infarction (MI) was evaluated in 1005 smokers and 2008 non-smokers. During the follow-up MI developed in 50 smokers and in 20 non-smokers.

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>No MI</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>50</td>
<td>955</td>
<td>1005</td>
</tr>
<tr>
<td>Non smokers</td>
<td>20</td>
<td>1988</td>
<td>2008</td>
</tr>
</tbody>
</table>

$I_e = \frac{50}{1005} = 0.04975$

$I_{ne} = \frac{20}{2008} = 0.00996$

$a/a+b$
RR = \frac{I_e}{I_{ne}} = 0.04975/0.00996 = 4.99 \quad 95\% \text{ CI: } 2.99-8.34

Upper 95\% CI = e^{\ln (4.99) + 1.96\sqrt{\frac{1}{50} - \frac{1}{1005} + \frac{1}{20} - \frac{1}{2008}}} = 8.34

Lower 95\% CI = e^{\ln (4.99) - 1.96\sqrt{\frac{1}{50} - \frac{1}{1005} + \frac{1}{20} - \frac{1}{2008}}} = 2.99

AR = I_e - I_{ne} = 0.04975 - 0.00996 = 0.03979

**Strengths of cohort studies:**
- Can be used to study multiple outcomes of a particular exposure
- Particularly good for the study of rare exposures
- Can elucidate temporal relationship between exposure and disease and thus give some indication of causality
- Allow direct measurement of incidence of disease in the exposed and non-exposed groups
- Minimizes bias in the ascertainment of exposure

**Limitations of cohort studies:**
- Not very good for the evaluation of rare diseases, unless the attributable risk is high and/or a very large sample size is considered
- If prospective, can be extremely expensive and time consuming
- If retrospective, require the availability of adequate records
- Validity of the results can be affected by losses to follow-up
- Generally require a large number of subjects

As an example of a cohort study, we can use a paper of Prescott E. et al. 1998 that tested association between smoking and risk of myocardial infarction.

**Smoking and risk of myocardial infarction in women and men: longitudinal population study.**

**Objective:**
To compare risk of myocardial infarction associated with smoking in men and women, taking into consideration differences in smoking behavior and a number of potential confounding variables.

**Design and setting:**
*Prospective cohort study* with follow up of myocardial infarction.
Pooled data from three population studies conducted in Copenhagen.

**Subjects:**
11,472 women and 13,191 men followed for a mean of 12.3 years.

**Main outcome measures:**
First admission to hospital or death caused by myocardial infarction.

**Results:**
1251 men and 512 women had a myocardial infarction during follow up. Compared with non-smokers, female current smokers had a relative risk of myocardial infarction of 2.24 (range 1.85-2.71) and male smokers 1.43 (1.26-1.62); ratio 1.57 (1.25-1.97). Relative risk of myocardial infarction increased with tobacco consumption in both men and women and was higher in inhalers than in non-inhalers. The risks associated with smoking, measured by both current and accumulated tobacco exposure, were consistently higher in women than in men and did not depend on age. This sex difference was not affected by adjustment for arterial blood pressure, total and high density lipoprotein cholesterol concentrations, triglyceride concentrations, diabetes, body mass index, height, alcohol intake, physical activity, and level of education.

**Conclusion:**
Women may be more sensitive than men to some of the harmful effects of smoking. Interactions between components of smoke and hormonal factors that may be involved in development of ischemic heart disease should be examined further.
References:

8. Levin KA. Study design IV. Cohort studies. Evidence-Based Dentistry 2003; 7:51-52
9. Levin KA. Study design I. Evidence-Based Dentistry 2005; 6:78–79
10. Levin KA. Study design V. Case–control studies. Evidence-Based Dentistry 2003; 7:83-84
11. Levin KA. Study design II. Issues of chance, bias, confounding and contamination. Evidence-Based Dentistry 2005; 6:102–103
1.4 EXPERIMENTAL EPIDEMIOLOGY

In experimental studies the researcher has control over the circumstances from the start, means that investigator actively assigns exposure to an investigated population. The effects of an intervention are measured by comparing the outcome in the experimental group with that in a control group. An intervention could include a medical or surgical intervention, a new drug, or an intervention to change lifestyle.

Experimental studies are less susceptible to confounding then observational studies because the investigator determines who is exposed and who is unexposed. If exposure is allocated randomly and the number of individuals randomised is large then even unrecognised confounding effects become statistically unlikely.

An interventional study is usually designed as a randomized controlled clinical trial, a field trial, or a community trial. Field trials involve people who are healthy but presumed to be at risk; data collection takes place “in the field”, usually among non-institutionalized people in the general population and population is randomised to preventive intervention or control group without intervention. In community trials the treatment groups are communities rather than individuals.

1.4.1 Clinical trials

Clinical trials are clinical research studies to determine whether biomedical or behavioral interventions are safe, efficacious, and effective. Moreover, it can provide evidence of reversibility or preventability of a disease by removal or reduction of related exposure by intervention and thus may add to understanding of causal relationship between a risk factor and disease.

In a clinical trial the direct comparison of two or more treatment modalities is performed. Based on way how participants are allocated to intervention clinical trials are either non-randomized or randomized, which are prefered. In non-randomized trial investigators assign participants to treatment groups, in randomized trial participants are allocated to intervention purely by the play of chance. Randomization maximizes the probability of similar background characteristics in compared groups and avoids selection and confounding biases.

The most common experimental design and a gold standard in medical research is the randomized controlled trial (RCT). An RCT (fig.6) is a true experiment (trial) in that the investigator controls the exposure and, in its simplest form, assigns subjects randomly to the experimental or control group (which may receive no treatment, the conventional treatment, or a placebo). However, in a proper controlled trial, the intervention is compared to a reference treatment, that can be the conventional treatment, a surgical procedure, placebo or a different dose of the same intervention. Both groups are followed and assessed in a rigorous comparison of their rates of morbidity, mortality, adverse events, functional health status, and quality of life. The main parameter that is measured at the end of the study to see whether the intervention worked is called the primary end point. RCTs need not be limited to two groups; a number of different treatment regimens may be compared at once. Administration of the intervention is preferably conducted in a blinded fashion. In a single-blind trial subjects included in the trial does not know which treatment they are given but the investigator does. In a double-blind trial both the investigators and the subjects included in the trial do not know which treatment is assigned. Sometimes both the investigators and the subjects know which treatment is actually given and this is called open trial. The results of a triple-blind trial, when patients, researchers and statisticians are “blinded” are decoded only at the end of the study.
Although study subjects are assigned to a particular treatment at the beginning of a randomized trial, they may discontinue therapy or change therapy during the study. In analysis of data we can remove subjects from the study when they discontinue or switch therapy (censoring), analyze subjects according to the treatment they are receiving at the time they develop the study outcome (as-treated analysis) or preferentially analyze subjects according to their initial treatment assignment and ignore switching that occurs during the trial (intention-to-treat analysis).

Analysis of randomized trial data is similar to the analysis of cohort study data. Incidences of the outcome for each treatment group are calculated and then compared using the relative risk or the risk difference. Clinically relevant is that we can estimate how many patients would need to be treated with the intervention (new drug...) instead of the reference treatment to prevent a single outcome (primary end point). This is called number needed to treat (NNT).

\[ NNT = \frac{1}{\text{risk difference}} \]

RCTs are most commonly used in therapeutic trials but can also be used in trials of prevention.

According to purposes there can be several trials. Treatment trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy. Prevention trials look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes. Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition. Screening trials test the best way to detect certain diseases or health conditions. Quality of Life trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness. Before entering studies written informed consent of all participants is needed.
Phases of intervention studies. Once a new pharmaceutical treatment has been developed, it undergoes testing in a sequence of phases before it can be approved by regulatory agencies for public use. Phase I and phase II studies evaluate the tolerability and biologic activity of a drug and phase III and phase IV studies are randomized trials that evaluate clinical endpoints.

In **Phase I trials**, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects, rather than to try to treat a condition. These trials usually involve healthy volunteers or sometimes patients. In **Phase II trials**, the experimental study in which drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. In **Phase III trials**, the experimental study in which drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely. In **Phase IV trials**, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

**Strengths of clinical trials:**
- Randomisation avoids selection and confounding biases
- Uniform collection of data
- Blinding of participants can reduce distortion in assessment of outcomes
- Ability to make causal inferences

**Limitations of clinical trials:**
- Subject exclusions may limit ability to generalize findings to other patients
- A long time for conclusion
- A large number of subjects usually required
- Typically high cost
- Ethical concerns
- Subjects may not comply with treatment

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**Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)**

[No authors listed]

**Abstract**

Drug therapy for hypercholesterolemia has remained controversial mainly because of insufficient clinical trial evidence for improved survival. The present trial was designed to evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary heart disease (CHD). 4444 patients with angina pectoris or previous myocardial infarction and serum cholesterol 5.5-8.0 mmol/L on a lipid-lowering diet were randomized to double-blind treatment with simvastatin or placebo. Over the 5.4 years median follow-up period, simvastatin produced mean changes in total cholesterol, low-density-lipoprotein cholesterol, and high-density-lipoprotein cholesterol of -25%, -35%, and +8%, respectively, with few adverse effects. 256 patients (12%) in the placebo group died, compared with 182 (8%) in the simvastatin group. The relative risk of death in the simvastatin group was 0.70 (95% CI 0.58-0.85, p = 0.0003). The 6-year probabilities of survival in the placebo and simvastatin groups were 87.6% and 91.3%, respectively. There were 189 coronary deaths in the placebo group and 111 in the simvastatin group. The relative risk of death in the simvastatin group was 0.58 (95% CI 0.46-0.73), while non-cardiovascular causes accounted for 49 and 46 deaths, respectively. 622 patients (28%) in the placebo group and 431 (19%) in the simvastatin group had one or more major coronary events. The relative risk was 0.66 (95% CI 0.59-0.75, p < 0.00001), and the respective probabilities of escaping such events were 70.5% and 79.6%. This risk was also significantly reduced in subgroups consisting of women and patients of both sexes aged 60 or more. Other benefits of treatment included a 37% reduction (p < 0.00001) in the risk of undergoing myocardial revascularisation procedures. This study shows that long-term treatment with simvastatin is safe and improves survival in CHD patients. (Lancet. 1994 Nov 19;344(8934):1383-9)
Field trials (community trials). While clinical trials are used to test therapeutic intervention, field trials are used to test primary prevention (vaccination, nutrition supplementation, etc.). The largest formal human experiment ever conducted, the Salk vaccine trial of 1954 for poliomyelitis prevention, is a prominent example. In this intervention type of study, the exposure is assigned to groups of people rather than singly, e.g. fluoridation trials in the 1940s and 1950s in U.S.A. that evaluated the effect of fluoride in a community water supply for dental caries prevention.

The natural experiment is not an actual experiment but, rather a cohort study that simulates what would occur in the changed natural conditions, e.g. as a sequel of disasters.

References:
8. Levin KA. Study design VII. Randomised controlled trials. Evidence-Based Dentistry 2007; 8:22-23
1.5 EPIDEMIOLOGIC SURVEILLANCE

1.5.1 Definition and aims

Managing programs of prevention or control of specific diseases need reliable information about the status of diseases or their antecedents in the population. The process that is used to collect, manage, analyze, interpret, and report this information/data is called surveillance. This epidemiologic survey is a modern system of epidemiologic activity with the aim of systematic long-term (for decades) follow up of specific disease together with all aspects influencing occurrence of this disease in the certain population by monitoring determinants of the region, time, natural or social factors, age, gender, employment of cases, etc.

A surveillance system should be designed to meet the needs of a prevention and control program, e.g. monitoring changes in incidence (malaria, TB, dengue fever) or associated risk factors (food and water sanitation) and of regulations or laws modified or initiated to address public health concerns (alcohol-related motor vehicle injuries, etc.).

Populations under surveillance are defined by the information needs of prevention or control programs (e.g. hospital program to monitor and reduce hospital acquired infections, global population in the case of emergence of influenza strains). For public health agencies, the population under surveillance usually represents residents within their jurisdiction, which may be a city, region or nation. In some cases, target population may be animals, e.g. animal surveillance for avian influenza, West Nile virus, recognizing that these pathogens of concern to human health also infect animals and may serve to alert public health authorities of potential transmission to humans.

Surveillance is often used to describe health problems themselves, including notification of cases, severity and manifestations of the disease, the nature and type of etiologic agents (e.g. typing by molecular methods, antibiotic resistance patterns of microorganisms), to follow possible evolutionary change of germs or the use and effect of treatments. The surveillance system for outbreaks of reported infections provides valuable information to document the epidemiology of these epidemics, to follow the changes of associated morbidity and mortality and to assess the impact of national policies in order to guide public health actions. For these purposes, it is advisable to introduce and validate the most modern tests for the surveillance of infections (nucleic acids testing, genotyping, sequencing, etc.).

Surveillance, generally considered the foundation of public health disease control efforts and among the most essential of public health functions, has various interrelated functions. Most of the surveillance done on a routine basis is passive surveillance, in which physicians, laboratories, and hospitals are required to report disease and appropriate data. Active surveillance is more labor, intensive and costly intended process for collecting data from proper investigations, studies and samplings.

These surveillance systems are networks of people and activities that maintain this process. They are operated by public health agencies and may function at local, national to international levels. Harmonization of systems, consistency of data with high quality and comparability of data are needed.

Establishing surveillance is often a first step to inform priority setting for new programs (vaccination, healthy diet, regular physical activities, etc.) and over time it is used to identify changes in the nature or extent of health problems. It requires statement of objectives, definition of the disease or condition under surveillance, and implementation of procedures for collecting, interpreting, and disseminating information. Thus surveillance systems may grow from simple ad hoc arrangements into more elaborate structures with evaluation of the effectiveness of public health interventions.
1.5.2 Performance of surveillance - phases:

1. **Collection of data:**
   - demographic (population health statistics are an important source of information for health measuring, decision makers and researchers in public health)
   - epidemiologic - case definition, notification of cases - inpatients and outpatients, burden of the disease – morbidity data -its incidence or prevalence, field trials, clinical data, laboratory results, hospital discharge data
   - environmental data - e.g. pollution of air, quality of surface water, infection in animal reservoirs, density of live vectors, etc.

   **Collection of data in standard format,** processing of data and activities are operated by public health agencies on local (county, city, district) level and are provided to the national public health service or to national **registries** (cancer data, tuberculosis, cardiovascular diseases, diabetes). Data coming from traditional **case reporting** provide epidemiologic parameters of time, place and person (descriptive information) by calculation incidence rates and prevalence, identify groups at highest risk, mortality rate and other rates. Surveillance data are then entered by the health authorities in a web-based entry application hosted at the **National Public Health Surveillance**.

   Surveillance may be also initiated to **identify risk factors** associated with disease and to suggest **hypotheses for further investigation**, cases identified by this system could be used in case-control studies (early studies in AIDS epidemic) and effective preventive actions were formulated based on such research, even before etiologic agent was discovered (HIV/AIDS infection).

2. **Analysis and interpretation of data** for description of actual situation of disease occurrence targeted to propose measures leading to lower incidence of this disease, risk factors, etc.

3. **Reporting, provision of information and communication** with public health workers for the best management of public health programs and direction of public health policy. **The information must be routinely disseminated** to a targeted audience that includes those stakeholders involved in reporting and those responsible for control programs.

4. Data can also be used to estimate the **implementation of recommended infection control measures and evaluate their effectiveness.** Results of national surveillance could be the basis for introduction of e.g. new vaccination approach or to activities to lower prevalence of risk factors of some chronic diseases (high blood pressure, cancer, obesity, etc.) or to estimation of the population group with higher risk to specific disease.

   **Feedback** is an important component of continuous surveillance with an organizational structure, which effectivity depends also on the resources available (number of personnel, level of training, technology, number of diseases, variables).

5. Traditionally, **surveillance systems have to be periodically evaluated.** It should include a review of their objectives, a detailed description of their operation, an assessment of their performance and recommendations. The performance of surveillance system can be judged by using a series of attributes, as sensitivity, timeliness, representativeness, positive predictive value, acceptability, flexibility, simplicity and costs.

1.5.3 International surveillance

**International surveillance** is coordinated by continental health organizations (e.g. CDC for Americas, ECDC for Europe, etc.) and finally on global scale by WHO. The effectiveness of this common approach and international cooperation according
to international regulations was confirmed in fighting against *small pox* resulting in its *eradication*. Similar situation is now in eradication of poliomyelitis and control and monitoring of circulating influenza strains with high capacity of antigenic changes emerging of new highly pathogenic agents, epidemics or even pandemics. Investigation of current influenza strains serves for preparing vaccine against actual antigenic composition of these viral strains.

ECDC has been collecting disease surveillance data from EU Member States on more than 50 communicable diseases and conditions using the European Surveillance System, known as TESSy (The Epidemiologic Surveillance System). The activities include annual data collection, analysis, dissemination of relevant scientific and technical data, promotion of the harmonization, external quality assurance (EQA) of laboratory methods and improvement of the laboratory performance.

Growing problem of spreading resistance of microbes causing nosocomial and community infections is in Europe under the control of the European Antimicrobial Resistance Surveillance System (EARSS).

Network of surveillance system on zoonoses, zoonotic agents, antimicrobial resistance, microbiological contaminants and food-borne outbreaks help by collecting and analyzing data to ensure European food safety risk assessment with European Food Safety Authority (EFSA).

Some diseases could be monitored by *sentinel surveillance*, when giving data from follow up of the selected group of population can be estimated the distribution or spread of this disease in the whole population. For example, spreading of HIV/AIDS infection in Africa is evaluated from morbidity rate of pregnant women.

Strategies for control and prevention may be quite different for various *emerging infections or re-emerging diseases*. Active and passive surveillance systems with rapid reporting and analysis of data are essential for the early detection of outbreaks, changes in epidemiology, and other events of public health concern. Such global surveillance system guided by WHO is *Global Outbreak Alert and Response Network* (GOARN) or *Early Warning and Response System* (EWRS) in the European Union.

Effective vaccinations are available only for some infections and are usually lacking for newly emerging infections. For the majority of emerging infections, control and prevention have to rely on information, education and exposure prophylaxis, interruption of transmission by vector control, control of reservoir hosts (e.g., rodents) and case finding with early diagnosis and treatment.

**Some examples of surveillance of special concern:**

Human infection with *seasonal influenza* and other non-seasonal *influenza viruses A*, such as H5N1, avian influenza A (H7N9) and other subtypes of avian influenza viruses WHO closely monitors together with occurrence in birds. Simultaneously risk assessments with potential public health impacts have been done by this health organization. Due to the constantly evolving nature of influenza viruses, WHO continues to stress the importance of global surveillance to detect virological, epidemiological and clinical changes associated with circulating influenza viruses that may affect human (or animal) health. Altogether, the five categories of influenza surveillance (*Virological Surveillance, Surveillance for Novel Influenza A Viruses, Outpatient Influenza-like Illness Surveillance Network -ILINet, Hospitalization Surveillance, Mortality Surveillance, Summary of the Geographic Spread of Influenza*) are designed to provide a national but also international picture of influenza activity.

Poliomyelitis is a crippling, life-threatening disease caused by the polio viruses types 1, 2, 3. This disease is transmitted through contaminated food and water, and
mostly affects children under the age of five. The most severe is paralysis and permanent disability occurring in some cases. Polio was a huge public health problem worldwide, until a vaccine was developed in 1957. In 1988 WHO adopted a resolution for the worldwide eradication of polio by launching of the Global Polio Eradication Initiative (GPEI). Since then, polio has decreased by 99% worldwide. **Surveillance of polio** permanently done on national and international levels include data about level of vaccination coverage by oral or inactivated vaccines, reporting of cases of acute flaccid paralysis with very precise diagnostic approach (sampling stools, immune status reflecting antibodies against polio viruses, vaccination). Surveillance included also prospective and retrospective screening of sewage water with typing of detected poliovirus, detection of possible importation, subsequent transmission and interruption of chains of transmission. All these procedures require a high level of integration of multiple surveillance strategies performed in parallel over extended periods of time to increase reliability and strengthen interpretation of data. In 1994, the WHO Region of the Americas was certified polio-free, followed by the WHO Western Pacific Region in 2000 and by the WHO European Region in June 2002. Transmission of the type 2 of wild poliovirus had been successfully stopped in 1999. Since 2013 only three countries have remained polio-endemic: Nigeria, Pakistan and Afghanistan. Populations in these countries can be difficult to reach due to war, geographic instability of their people, and poor health infrastructure. In May 2012 WHO adopted a new resolution declaring the completion of polio eradication (Polio Eradication and Endgame Strategic Plan 2013-2018). Data from this surveillance system informed the country’s medical surveillance officers, government officials, and thousands of volunteer vaccinators of the areas of highest risk important for distribution of the vaccines.

In most countries, the global effort has expanded capacities to **tackle other infectious diseases** by building effective surveillance and immunization systems.

**Measles surveillance** which includes establishing case-based surveillance with laboratory testing of persons with suspected measles to confirm cases and outbreaks and to identify measles virus genotypes must be enforced in Europe together with vaccination coverage to achieve goal of elimination of measles very early.

Under the past and on-going epidemiologic transitions the **modern concept of surveillance** was shaped by programs to combat infectious diseases, now it reflects the diversity of epidemiologic inquiry, including acute and chronic diseases, reproductive health, injuries, disabilities, environmental and occupational health hazards and health risk behaviors. Surveillance will have to be strengthened globally to track exposure to risk factors for the major causes of disability and death, disease outcomes, and health systems responses.

**Disease registries** are comprehensive longitudinal listings of people with particular conditions, including detailed information about diagnostic classification, treatment and outcome. Registries were initially established primary for epidemiologic research, then they have been used to ensure the provision of appropriate care, later for evaluation of the effectiveness of targeted screening programs. To focus on selected diseases (oncologic diseases, births defects, etc.) and conditions, registries often develop a constituency that promotes participation and reporting (numerous sources of data from medical doctors, laboratories, etc.).
References:


7. WHO-Regional Office for Europe: Eliminating Measles and Rubella –Framework for the verification process in the WHO European Region, WHO-Regional Office for Europe, 2012, 25 pp
2 EPIDEMIOLOGY OF CHRONIC CIVILISATION DISEASES AND PREVENTION

2.1 EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES

2.1.1 Classification, epidemiological characteristics and importance of cardiovascular diseases

Cardiovascular disease (CVD) is a broad class of diseases that involve impairments of the heart and blood vessels. This group includes coronary heart or artery diseases (CHD or CAD) such as angina and myocardial infarction (commonly known as a heart attack). Other CVDs are stroke, hypertensive heart disease, rheumatic heart disease, peripheral artery disease, congenital heart disease and others. A wide range of clinical manifestations are related to atherosclerosis. Atherosclerosis is a chronic and progressive disease morphologically characterized as asymmetric focal thickenings of the intima in primarily large and medium-sized elastic and muscular arteries, such as aorta, coronary, carotid, and femoral arteries. Atherosclerotic cardiovascular disease (CVD) is a chronic disorder developing insidiously throughout life and usually progressing to an advanced stage by the time symptoms occur. It can be presented chronically, such as stable angina pectoris, or can manifest suddenly with myocardial infarction (MI) or stroke with or without preceding clinical symptoms. Coronary heart disease (CHD) and stroke are the main and most important forms of CVD.

CVDs are the main cause of death globally and are responsible for 46% of all non-communicable diseases deaths. These diseases are the leading fatal cause in all areas of the world except Africa. Together they resulted in 17.3 million deaths (31.5%) in 2013 up from 12.3 million (25.8%) in 1990. More than 3 million of these deaths occurred before the age of 60 and could have largely been prevented. The percentage of premature deaths from CVDs ranges, over three quarters of CVD deaths occurs in low and middle-income countries. It is also estimated that by 2030, over 23 million people will die from cardiovascular diseases each year. Mortality of CVDs has been increasing in much of the developing countries, while rates have declined in most of the developed world since the 1970s mainly in high-income countries.

CHD is the leading cause of death worldwide and moreover it is on the rise and has become a true pandemic. CHD and stroke account for 80% of CVD deaths in males and 75% of CVD deaths in females. The average age of death from CHD in the developed world is around 80 while it is around 68 in the developing world. Disease onset is typically seven to ten years earlier in men as compared to women.

CVDs remains the major cause of premature death in Europe, even though CVD mortality has fallen considerably over recent decades in many European countries. In Europe almost half of all deaths from CVD are from CHD and nearly a third in women and a quarter in men are due to stroke.
Regional differences in dynamic of pattern, magnitude and timing of CVD have been noted in different parts of the world. Cardiovascular disease affects low- and middle-income countries even more than high-income countries.

Cardiovascular diseases are the main cause of mortality in almost all OECD countries, and accounted for 35% of all deaths in 2009. A decline in age-standardized CHD and CVD mortality has been observed in many European countries between the 1970s and 1990s; this pattern has been evident mainly in the more affluent countries.

However, CVD still remains a major cause of mortality in Europe, causing almost 4.1 million deaths per year, or 46% of all deaths in Europe (Tables 3, 4). On the other hand, the observed decline in CVD illustrates the potential for prevention of premature deaths and for prolonging healthy life expectancy. In several central and eastern European countries, however, CVD and CHD mortality is still high. Geographically also a gradient in CHD between Western European countries and Southern European countries is evident, with generally higher rates in Western European countries. Death rates from stroke are higher in Central and Eastern Europe compare to the rest of the Europe.

Over the past decades there were very large consistent declines in cardiovascular disease, and especially in CHD, across the European Union (in most Northern and Western European countries), with rates of CVD mortality falling by >30% in both sexes and CHD mortality falling by a third in men and over a quarter in women between 1985–89 and 2000–2004.

These trends have been attributed to improved clinical management, as well as improved primary prevention and risk factor management which has reduced incidence rates of disease. Since the beginning of the new millennium, however rates are also falling in the majority of Central and Eastern European countries. Also decline in death rates from stroke is evident in most European countries with few exceptions (Poland and Slovakia).

Table 3. Number and percentage of deaths from cardiovascular diseases in Europe

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular disease (total)</th>
<th>Coronary heart disease</th>
<th>Cerebrovascular disease</th>
<th>Other cardiovascular diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Total deaths (all ages)</td>
<td>1,862,004</td>
<td>2,222,657</td>
<td>876,478</td>
<td>905,706</td>
</tr>
<tr>
<td>Premature deaths—before age 75</td>
<td>946,280</td>
<td>544,769</td>
<td>477,833</td>
<td>237,673</td>
</tr>
<tr>
<td>Premature deaths—before age 65</td>
<td>508,228</td>
<td>202,175</td>
<td>253,734</td>
<td>77,477</td>
</tr>
<tr>
<td></td>
<td>1,348,284</td>
<td>1,747,424</td>
<td>702,211</td>
<td>796,454</td>
</tr>
<tr>
<td>Premature deaths—before age 75</td>
<td>807,623</td>
<td>412,803</td>
<td>434,582</td>
<td>218,271</td>
</tr>
<tr>
<td>Premature deaths—before age 65</td>
<td>505,522</td>
<td>199,862</td>
<td>296,610</td>
<td>102,918</td>
</tr>
<tr>
<td></td>
<td>1,209,145</td>
<td>1,318,666</td>
<td>628,192</td>
<td>691,583</td>
</tr>
<tr>
<td></td>
<td>4084,661</td>
<td>4928,224</td>
<td>2,182,184</td>
<td>2,106,359</td>
</tr>
<tr>
<td>Premature deaths—before age 75</td>
<td>1,491,049</td>
<td>1,751,506</td>
<td>1,361,396</td>
<td>1,474,147</td>
</tr>
<tr>
<td>Premature deaths—before age 65</td>
<td>710,403</td>
<td>331,211</td>
<td>314,477</td>
<td>150,477</td>
</tr>
</tbody>
</table>


Interestingly, trends in the prevalence of major cardiovascular risk factors are different with particularly increasing pattern for obesity and diabetes and plateau after substantial declines for hypertension. The trends even vary widely between countries and age groups. Smoking is of great concern in Europe and although smoking rates have
declined in many European countries, the decline is now slow and in some countries rates remain stable or are increasing, particularly among women. In fact, women are now smoking nearly as much as men in many countries and girls often smoke more than boys.

Low level of physical activity in majority of Europeans, with inactivity more common among women than men, contributes to CVD risk. Fruit and vegetable consumption in Europe has increased in last decades, however overall fat intake has remained stable. Low socio-economic status, stress, depression, anxiety and the type D personality contribute to the CVD risk.

Table 4. Age-standardized death rates from cardiovascular disease and coronary heart disease by country and sex (per 100 000 population)

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Males CVD total</th>
<th>Males CHD</th>
<th>Females CVD total</th>
<th>Females CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>2004</td>
<td>490.7</td>
<td>209.3</td>
<td>97.8</td>
<td>156.5</td>
</tr>
<tr>
<td>Armenia</td>
<td>2009</td>
<td>640.4</td>
<td>298.0</td>
<td>164.7</td>
<td>407.4</td>
</tr>
<tr>
<td>Austria</td>
<td>2011</td>
<td>240.7</td>
<td>87.1</td>
<td>45.3</td>
<td>125.1</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>2007</td>
<td>616.8</td>
<td>363.0</td>
<td>190.6</td>
<td>149.3</td>
</tr>
<tr>
<td>Belarus</td>
<td>2009</td>
<td>892.7</td>
<td>563.9</td>
<td>316.2</td>
<td>642.2</td>
</tr>
<tr>
<td>Belgium</td>
<td>2005</td>
<td>205.7</td>
<td>86.6</td>
<td>47.7</td>
<td>76.3</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>2011</td>
<td>474.7</td>
<td>201.5</td>
<td>119.3</td>
<td>93.5</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>2011</td>
<td>732.4</td>
<td>384.5</td>
<td>219.8</td>
<td>145.6</td>
</tr>
<tr>
<td>Croatia</td>
<td>2011</td>
<td>415.9</td>
<td>179.2</td>
<td>93.0</td>
<td>195.1</td>
</tr>
<tr>
<td>Cyprus</td>
<td>2011</td>
<td>228.4</td>
<td>95.3</td>
<td>54.6</td>
<td>102.2</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>2011</td>
<td>412.9</td>
<td>182.1</td>
<td>92.1</td>
<td>219.9</td>
</tr>
<tr>
<td>Denmark</td>
<td>2006</td>
<td>243.8</td>
<td>99.5</td>
<td>50.4</td>
<td>97.7</td>
</tr>
<tr>
<td>Estonia</td>
<td>2011</td>
<td>510.1</td>
<td>270.0</td>
<td>142.0</td>
<td>255.6</td>
</tr>
<tr>
<td>Finland</td>
<td>2011</td>
<td>275.8</td>
<td>126.1</td>
<td>68.5</td>
<td>165.5</td>
</tr>
<tr>
<td>France</td>
<td>2009</td>
<td>155.8</td>
<td>64.8</td>
<td>37.0</td>
<td>49.7</td>
</tr>
<tr>
<td>Georgia</td>
<td>2010</td>
<td>325.1</td>
<td>196.8</td>
<td>108.7</td>
<td>80.3</td>
</tr>
<tr>
<td>Germany</td>
<td>2011</td>
<td>231.0</td>
<td>93.5</td>
<td>49.7</td>
<td>103.0</td>
</tr>
<tr>
<td>Greece</td>
<td>2010</td>
<td>251.9</td>
<td>115.6</td>
<td>69.7</td>
<td>89.1</td>
</tr>
<tr>
<td>Hungary</td>
<td>2011</td>
<td>516.2</td>
<td>273.3</td>
<td>155.0</td>
<td>275.2</td>
</tr>
<tr>
<td>Iceland</td>
<td>2009</td>
<td>218.6</td>
<td>79.7</td>
<td>40.2</td>
<td>117.5</td>
</tr>
<tr>
<td>Ireland</td>
<td>2009</td>
<td>237.9</td>
<td>101.9</td>
<td>50.3</td>
<td>143.7</td>
</tr>
<tr>
<td>Israel</td>
<td>2010</td>
<td>144.9</td>
<td>58.5</td>
<td>28.1</td>
<td>70.3</td>
</tr>
<tr>
<td>Italy</td>
<td>2010</td>
<td>196.4</td>
<td>69.9</td>
<td>36.5</td>
<td>76.9</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>2010</td>
<td>809.8</td>
<td>534.9</td>
<td>319.2</td>
<td>264.9</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>2010</td>
<td>841.8</td>
<td>478.5</td>
<td>260.7</td>
<td>534.2</td>
</tr>
<tr>
<td>Latvia</td>
<td>2010</td>
<td>674.7</td>
<td>405.3</td>
<td>230.6</td>
<td>375.4</td>
</tr>
<tr>
<td>Lithuania</td>
<td>2010</td>
<td>667.0</td>
<td>352.3</td>
<td>202.5</td>
<td>436.2</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>2010</td>
<td>211.2</td>
<td>79.4</td>
<td>42.4</td>
<td>68.8</td>
</tr>
<tr>
<td>Malta</td>
<td>2011</td>
<td>288.6</td>
<td>113.9</td>
<td>55.0</td>
<td>177.4</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2011</td>
<td>170.9</td>
<td>66.4</td>
<td>34.0</td>
<td>54.6</td>
</tr>
<tr>
<td>Norway</td>
<td>2011</td>
<td>183.6</td>
<td>67.8</td>
<td>33.2</td>
<td>82.5</td>
</tr>
<tr>
<td>Poland</td>
<td>2011</td>
<td>415.3</td>
<td>211.5</td>
<td>119.4</td>
<td>128.2</td>
</tr>
<tr>
<td>Portugal</td>
<td>2011</td>
<td>174.7</td>
<td>71.0</td>
<td>37.3</td>
<td>49.1</td>
</tr>
<tr>
<td>Republic of Moldova</td>
<td>2011</td>
<td>797.3</td>
<td>414.3</td>
<td>205.9</td>
<td>530.1</td>
</tr>
<tr>
<td>Romania</td>
<td>2010</td>
<td>647.3</td>
<td>311.5</td>
<td>164.2</td>
<td>238.3</td>
</tr>
</tbody>
</table>
2.1.2 Risk factors of CVD

Different factors play role in the risk of CVD. In general we can divide them into non-modifiable and modifiable. Genetics, family history, age and sex are non-modifiable risk factors that can substantially influence the risk. Increasing age and male sex increase CVD risk and are used to stratify risk assessments. On the other hand CVD is by far the biggest cause of death in women; in Europe 51% of women die from CVD compared with 42% of men. Certain genetic disorders such as familial hypercholesterolemia are known to dramatically increase the risk of CVD. Most cardiovascular disease affects older adults.

In the United States 11% of people between 20 and 40 have CVD, while 37% between 40 and 60, 71% of people between 60 and 80, and 85% of people over 80 have CVD.

Coronary heart diseases are 2 to 5 times more common among middle-aged men than women. One of the proposed explanations for gender differences in cardiovascular diseases is hormonal difference. Among women, estrogen may have protective effect, therefore men are at greater risk of heart disease than pre-menopausal women. Once past menopause, it has been argued that a woman's risk is similar to a man's. However, if a female has diabetes, she is more likely to develop heart disease than a male with diabetes.

However, many important cardiovascular risk factors are modifiable by lifestyle change, social change, drug treatment and prevention of hypertension, hyperlipidemia (high level of total and LDL cholesterol) and diabetes. CVD is strongly associated with behavioral risk factors - tobacco use, physical inactivity, unhealthy diet habits (high intakes of saturated fat, trans-fats, calories and salt), harmful use of alcohol and psychosocial stress (depression). Smoking is associated with increased risk of all types of CVD. Risks to health from tobacco use result not only from direct consumption of tobacco, but also from exposure to second-hand smoke. The effect of behavioral risk factors may lead to development of so called “intermediate risks factors” such as metabolic risk factors (increased blood pressure, blood glucose and lipids, overweight and
obesity, excess homocysteine). Among other risk factors social factors, as poverty and low educational status also could play role.

2.1.3 Prevention

According to the World Health Organization (WHO) over three-quarters of all CVD mortality may be prevented with adequate changes in lifestyle. Primary prevention including education and proper control of major modifiable risk factors (LDL cholesterol, hypertension, smoking, obesity and diabetes) is a cornerstone in CVD prevention. This is primarily focused on diet and lifestyle interventions, e.g. reduction in saturated fat, replacement with polyunsaturated fat. Lowering LDL cholesterol levels and blood pressure have been consistently shown to decrease CVD mortality and morbidity in several randomised clinical trials.

Taking the example of coronary heart disease (CHD), altogether 80% of the reduction in CHD mortality in Finland during 1972–1992 has been explained by a decline in the major risk factors. Similarly, in Ireland, almost half (48.1%) of the reduction in CHD mortality rates during 1985–2000 among those aged 25–84 years has been attributed to favorable trends in population risk factors. In both countries, the greatest benefits appear to have come from reductions in mean cholesterol concentrations, smoking prevalence and blood pressure levels.

Changes in the life-style and social risk factors are often related to the population CVD reduction strategies targeted at the population at large. National legislatives and health policies to ban smoking or reduce salt intake are good examples of this strategy. This population-wide approach may bring large benefits at the population level although it may offer little to the individual. Both population measures and improved access to individual health care interventions can result in a major reduction in the health and socioeconomic burden caused by these diseases and their risk factors. The impact of such an approach on the total number of cardiovascular events in the population may be large, because all subjects are targeted and a majority of events occur in the substantial group of people at only modest risk. Prevention of CVD should be long-life, ideally starting during pregnancy and lasting until the end of life.

At the individual level, for primary prevention individual health-care interventions need to be targeted to subjects with high total cardiovascular risk or with single risk factor (e.g. hypertension, hypercholesterolemia...). In those with established disease (secondary prevention) pharmacological treatment with aspirin, beta-blockers, angiotensin-converting enzyme inhibitors and statins is necessary. The benefits of these interventions are largely independent, but when used together with smoking cessation, nearly 75% of recurrent vascular events may be prevented. Under the leadership of the WHO, all Member States (194 countries) agreed in 2013 on global mechanisms to reduce the avoidable noncommunicable diseases (NCD) burden including a “Global action plan for the prevention and control of NCDs 2013-2020”. This plan aims to reduce the number of premature deaths from NCDs by 25% by 2025 through nine voluntary global targets. Two of the global targets directly focus on preventing and controlling CVDs.

In the 1980s and 1990s the MONICA project showed that only part of the variation in the time trends of coronary event rates could be predicted by trends in risk factors. In fact the changes in risk factors explained almost half the variation in event rates in men but less in women.

Estimation of effect of different intervention modalities (changes in coronary risk factors, treatment...) on CHD mortality has been evaluated also in models using data...
obtained from randomised clinical trials. Despite of an increase in the prevalence of obesity and type 2 diabetes a beneficial reduction in major risk factors (in particular smoking, blood pressure, and cholesterol) was attributed to more than half of the decrease in CHD deaths (Figure 7). Better treatments of acute myocardial infarction, heart failure, and other cardiac conditions account for about 40% of the decline in CHD death rates. Thus, it seems that more effective is preventive approach targeted to risk factors for decrement of mortality rate. According to various studies (Figure 7) this approach was successful in 44%-76% reduction of mortality rate of CHD. Mostly a decline in CHD mortality can happen rapidly also after individual or population-wide changes in diet or smoking as was shown during clinical trials and community experiments (e.g. The North Karelia Project - Finland).

Figure 7. Percentage of the decrease in deaths from coronary heart disease attributed to treatments and risk factor changes in different populations in years 1968-2002

source: Eur Heart J. 2012; 33: 1635–1701

It is essential for clinicians to be able to assess risk of CVD rapidly and with sufficient accuracy to allow logical management decisions. Risk charts such as SCORE, that use age, sex, smoking status, total cholesterol, and systolic blood pressure (SBP) to estimate the 10-year risk of a first fatal or non-fatal CHD event, are intended to facilitate risk estimation in apparently healthy persons. Patients who have had a clinical event such as an acute coronary syndrome (ACS) or stroke automatically qualify for intensive risk factor evaluation and management.

Despite of major improvements in recent years on cardiovascular disease prevention and treatment, cardiovascular disease continues to be a major contributor to mortality and disability in Europe and all over world. Both population and individual interventions should be thus focused to improve even more this situation and thus enhance health status of population and reduce a substantial burden that CVD places on the health care systems and economies. There have been major improvements in recent years on many measures of cardiovascular disease; however, these improvements have not been universal, and substantial inequalities persist.
References:
2.2 EPIDEMIOLOGY OF CANCER

2.2.1 Definition and scope of cancer epidemiology

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumors and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs. This process is referred to as metastasis. Metastases are the major cause of death from cancer.

Cancer epidemiology is the scientific discipline that studies the occurrence of human neoplastic diseases, their risk factors, and their distribution in populations.

Cancer epidemiology also encompasses the study of some clinical aspects of human cancer; such as disease recurrence, second tumors (new tumors in the same individual) death, as well as determinants of this development, the so-called prognostic factors.

Well accepted results of epidemiological investigations and experimental evidence from other disciplines form the essentials of cancer prevention strategies and have revealed the importance of risk factors such as tobacco smoking, unhealthy diet, professional and environmental exposures, and that of primary prevention and screening.

Typical for cancer being that development of manifested disease requires relatively very long time of exposure to carcinogens, in some cancer sites more than 20 years. Another characteristic is multifactorial etiology of cancer. On the other hand cancer is well specified and clearly defined group of diseases with exact classification.

2.2.2 Cancer disease classification

Neoplasms can be classified in many ways, but the most important classifications for the epidemiologist are those based on:
1) Topography - the site in the body where the tumor is located.
2) Morphology (or histology) - the microscopic characteristics of the tumor.
3) Behavior - the tendency to invade other tissues (malignant, benign, in situ, and uncertain).

Uniform definitions and uniform systems of classification are fundamental to the quantitative study of diseases. Without a standard classification tool that remains fixed for periods of time and is applied uniformly, meaningful comparative analyses of morbidity and mortality data would be impossible. The International Classification of Diseases (ICD), published by the World Health Organization, is such a standard classification tool. It is revised every ten years or so; the 10th revision (ICD -10) (WHO, 1992) is currently in use.

Although retaining the traditional structure of ICD-9, the 10th revision of the ICD uses an alphanumeric coding scheme - the first character of the category is a letter - replacing the numeric codes of ICD-9 and previous revisions. This change provides a larger coding frame and leaves scope for future inclusion of new disease entities without disrupting the numbering system.

ICD-10 has three volumes. Volume 1 deals with the tabular list of classification at the level of three and four characters, special tabulations of morbidity and mortality, and definitions and nomenclature regulations. Volume 2 is essentially an instruction manual. Volume 3 contains an alphabetical index.
The ICD chapter that deals with neoplasms presents a primarily topographic classification arranged according to the anatomical site of the tumor. Organs are ordered according to organ systems.

Neoplasms with a given behavior are grouped as malignant, benign, \textit{in situ} and of uncertain behavior.

**Classification of neoplasms according to ICD-10 (WHO, 1992).**

C00-C75 Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, hematopoietic and related tissue

- C00-C14 Lip, oral cavity and pharynx
- C15-C26 Digestive organs
- C30-C39 Respiratory and intrathoracic organs
- C40-C41 Bone and articular cartilage
- C43-C44 Skin
- C45-C49 Mesothelium and soft tissue
- C50 Breast
- C51-C58 Female genital organs
- C60-C63 Male genital organs
- C64-C68 Urinary tract
- C69-C72 Eye, brain and other parts of central nervous system
- C73-C75 Thyroid and other endocrine glands
- C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites
- C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue
- C97 Malignant neoplasms of independent (primary) multiple sites

D00-D09 \textit{In situ} neoplasms

D10-D36 Benign neoplasms

D37-D48 Neoplasms of uncertain or unknown behaviour

The first morphological classification was developed in 1951 and many others have since emerged (Table). The \textit{Manual of Tumor Nomenclature and Coding} (MOTNAC) (American Cancer Society, 1951; Percy \textit{et al.}, 1968) and, more recently, the \textit{International Classification of Diseases for Oncology} (ICD-O) (WHO, 1976; Percy \textit{et al.}, 1990) have been the most widely used. They provide not only morphology and behavior codes, but also topography codes that are directly related to the ICD codes. A full discussion of the merits and drawbacks of each of these classifications is given by Muir and Percy (1991). The major advantage of ICD is that it is truly international, being used by all WHO Member States for tabulating the causes of death and for most health statistics. The main disadvantage is that, for the majority of sites, no separation on the basis of morphology is possible. As a result, it is generally recommended that agencies interested in identifying both the site and morphology of tumors, like cancer registries and pathology laboratories, use ICD-O, which is a dual-axis classification providing independent coding systems for topography and morphology.

### 2.2.3 Sources of data

Routine data are derived from established data collection systems associated with the health and social services. In general, the data are not collected with the aim of answering any specific question. For whatever purpose they were collected, such data can often be used in epidemiological studies; these include data from censuses and population registers, birth and death certificates, cancer registrations, health information systems, medical and hospital records, etc. Routine data collection systems can...
provide information on the exposures and outcomes of interest in an epidemiological study. Two such systems - death certification and cancer registration - are particularly important in cancer epidemiology.

**Death certification**

Mortality data are usually based upon a standard death certificate, which records the date of death, cause of death, age, sex, date of birth and place of residence of the deceased. In addition, occupation and other information may be recorded. In most countries, death certificates are usually completed by a doctor or other health worker but in some cases this is done by the police or other authorities. Once certificates are completed, the cause of death is coded according to the *International Classification of Diseases*, now in its tenth revision (WHO, 1992). This is a hierarchical classification of diseases, from broad categories down to a detailed four-character classification.

Usually, only the underlying cause of death is coded and used in mortality statistics, although contributing causes may also be coded. While more complete and reliable than many routine sources of morbidity data, mortality data are still subject to some misclassification.

A large international study of 8737 cancer deaths in cities in England, USA and Latin America revealed that of deaths classified on the death certificate as caused by cancer, 20% were due to other causes, however, 24.6% of cancer deaths had been wrongly classified under other causes of death. On balance, therefore, total cancer mortality was only 4% underestimated in the official statistics derived from death certificates.

The degree of misclassification varied with cancer site, being greater for those that are more difficult to diagnose, such as primary liver cancer and brain tumours.

International cancer mortality statistics are published regularly by the World Health Organization (*World Health Statistics Annual series*).

**Cancer registration**

There are two types of cancer registry: hospital-based and population-based.

*Hospital-based cancer registries* record all cancer patients seen in a particular hospital. Their main purpose is to contribute to patient care and administrative management, although they may be useful to a certain extent for epidemiological purposes.

For instance, ‘rolling’ case-control studies may be set up to investigate the etiology of a particular cancer; this is achieved by comparing the characteristics of such cases with those of a control group, which may be made up of patients either with other types of cancer, or with other illnesses. Nevertheless, hospital-based registries cannot provide measures of the occurrence of cancer in the general population, because it is not possible to define the population from which cases arise.

*Population-based cancer registries* seek to record all new (incident) cancer cases that occur in a well defined population. As a result, they provide measures of the occurrence of cancer in their catchment population.

Population-based cancer registration has been developed in many countries to provide reasonably comparable data on cancer incidence and as a resource for epidemiological studies. Cancer incidence data from higher quality registers are compiled by the International Agency for Research on Cancer (IARC) in the series *Cancer Incidence in Five Continents*.

Some indicators of data quality for the different registries included in this publication are tabulated in these volumes. However, these are mostly indirect indicators of data quality: proportion of registrations verified histologically; proportion of cases registered on the basis of information on the death certificate only; proportion of cases with missing information, etc.
More systematic analyses of the validity of cancer registration data are available for certain registries, where a sample of cases was reabstracted and re-coded.

The majority of cancer registries collect information about cancer patients, such as their occupation, social class, country of birth, ethnicity, etc. Occurrence of cancer can therefore be examined in relation to these variables.

Cancer is the second leading cause of death worldwide, accounting for 8.2 million deaths in 2012. Lung, liver, stomach, colorectal and breast cancers cause the most cancer deaths each year: lung (1.59 million deaths), liver (745,000 deaths), stomach (723,000 deaths), colorectal (694,000 deaths), breast (521,000 deaths), esophageal cancer (400,000 deaths).

The most frequent types of cancer differ between men and women.

Ageing is a fundamental factor for the development of cancer. The incidence of cancer rises dramatically with age, most likely due to a buildup of risks for specific cancers that increase with age. The overall risk accumulation is combined with the tendency for cellular repair mechanisms to be less effective as a person grows older.

### 2.2.4 Risk factors

Cancer arises from one single cell. The transformation from a normal cell into a tumor cell is a multistage process, typically a progression from a pre-cancerous lesion to malignant tumors. These changes are the result of the interaction between a person's genetic factors and three categories of external agents, including:

- physical carcinogens, such as ultraviolet and ionizing radiation;
- chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin (a food contaminant) and arsenic (a drinking water contaminant);
- biological carcinogens, such as infections from certain viruses, bacteria or parasites.

WHO, through its cancer research agency, International Agency for Research on Cancer (IARC), maintains a classification of cancer causing agents.

Cancer risk factors worldwide involve mainly tobacco use, alcohol use, unhealthy diet and physical inactivity. Chronic infections from hepatitis B (HBV), hepatitis C virus (HCV) and some types of human papilloma virus (HPV) are leading risk factors for cancer in low- and middle-income countries. Cervical cancer, which is caused by HPV, is a leading cause of cancer death among women in low-income countries.

About 30% of cancer deaths are due to the five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, alcohol use.

Tobacco use is the most important risk factor for cancer causing over 20% of global cancer deaths and about 70% of global lung cancer deaths.

Cancer causing viral infections such as HBV/HCV and HPV are responsible for up to 20% of cancer deaths in low- and middle-income countries.

### Tobacco

Tobacco use is the single greatest avoidable risk factor for cancer mortality worldwide, causing an estimated 22% of cancer deaths per year. In 2004, 1.6 million of the 7.4 million cancer deaths were due to tobacco use.

Tobacco smoking causes many types of cancer, including cancers of the lung, esophagus, larynx (voice box), mouth, throat, kidney, bladder, pancreas, stomach and cervix. About 70% of the lung cancer burden can be attributed to smoking alone. Second-hand smoke (SHS), also known as environmental tobacco smoke, has been proven to
cause lung cancer in nonsmoking adults. Smokeless tobacco (also called oral tobacco, chewing tobacco or snuff) causes oral, esophageal and pancreatic cancer.

**Physical inactivity, dietary factors, obesity and overweight**

Dietary modification is another important approach to cancer control. There is a link between overweight and obesity to many types of cancer such as esophagus, colorectum, breast, endometrium and kidney. Diets high in fruits and vegetables may have a protective effect against many cancers. Conversely, excess consumption of red and preserved meat may be associated with an increased risk of colorectal cancer. In addition, healthy eating habits that prevent the development of diet-associated cancers will also lower the risk of cardiovascular disease.

Regular physical activity and the maintenance of healthy body weight, along with a healthy diet, will considerably reduce cancer risk. National policies and programs should be implemented to raise awareness and reduce exposure to cancer risk factors, and to ensure that people are provided with the information and support they need to adopt healthy lifestyles.

**Alcohol use**

Alcohol use is a risk factor for many cancer types including cancer of the oral cavity, pharynx, larynx, esophagus, liver, colorectum and breast. Risk of cancer increases with the amount of alcohol consumed. The risk from heavy drinking for several cancer types substantially increases if the person is also a heavy smoker.

Attributable fractions vary between men and women for certain types of alcohol-related cancer, mainly because of differences in average levels of consumption. For example, 22% of mouth and oropharynx cancers in men are attributable to alcohol whereas in women the attributable burden drops to 9%. A similar sex difference exists for esophageal and liver cancers.

**Infections**

Infectious agents are responsible for almost 22% of cancer deaths in the developing world and 6% in industrialized countries. Viral hepatitis B and C cause cancer of the liver; human papilloma virus infection causes cervical cancer; the bacterium *Helicobacter pylori* increases the risk of stomach cancer. Well known is association between HIV/AIDS infection and Kaposi sarcoma. In some countries the parasitic infection schistosomiasis increases the risk of bladder cancer. Preventive measures include vaccination against VHB and HPV infections and prevention of infection and infestation.

**Environmental pollution**

Environmental pollution of air, water and soil with carcinogenic chemicals accounts for 1–4% of all cancers (IARC/WHO, 2003). Exposure to carcinogenic chemicals in the environment can occur through drinking water or pollution of indoor and ambient air.

In Bangladesh, 5–10% of all cancer deaths in an arsenic-contaminated region were attributable to arsenic exposure. Inhalation of asbestos fibers is associated with risk of lung cancer development. Exposure to carcinogens also occurs via the contamination of food by chemicals, such as aflatoxins or dioxins. Indoor air pollution from coal fires doubles the risk of lung cancer, particularly among non-smoking women. Worldwide, indoor air pollution from domestic coal fires is responsible for approximately 1.5% of all lung cancer deaths. Coal use in households is particularly widespread in Asia.
**Occupational carcinogens**

More than 40 agents, mixtures and exposure circumstances in the working environment are carcinogenic to humans and are classified as occupational carcinogens. Those occupational carcinogens are causally related to cancer of the lung, bladder, larynx and skin, leukemia and nasopharyngeal cancer. Mesothelioma (cancer of the outer lining of the lung or chest cavity) is to a large extent caused by work-related exposure to asbestos.

Occupational cancers are concentrated among specific groups of the working population, for whom the risk of developing a particular form of cancer may be much higher than for the general population. About 20–30% of the male and 5–20% of the female working-age population (people aged 15–64 years) may have been exposed to lung carcinogens during their working lives, accounting for about 10% of lung cancers worldwide. About 2% of leukemia cases worldwide are attributable to occupational exposures.

**Radiation**

Ionizing radiation is carcinogenic to humans. Knowledge on radiation risk has been mainly acquired from epidemiological studies of the Japanese atom bomb survivors as well as from studies of medical and occupational radiation exposure cohorts. Ionizing radiation can induce leukemia and a number of solid tumors, with higher risks at young age at exposure.

Residential exposure to radon gas from soil and building materials is estimated to cause between 3% and 14% of all lung cancers, making it the second cause of lung cancer after tobacco smoke. Radon levels in homes can be reduced by improving the ventilation and sealing floors and walls.

Ionizing radiation is an essential diagnostic and therapeutic tool. To guarantee that benefits exceed potential radiation risks radiological medical procedures should be appropriately prescribed and properly performed, to reduce unnecessary radiation doses, particularly in children.

Ultraviolet (UV) radiation, and in particular solar radiation, is carcinogenic to humans, causing all major types of skin cancer, such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. Globally in 2000, over 200 000 cases of melanoma were diagnosed and there were 65 000 melanoma-associated deaths. Avoiding excessive exposure, use of sunscreen and protective clothing are effective preventive measures. UV-emitting tanning devices are now also classified as carcinogenic to humans based on their association with skin and ocular melanoma cancers.

**2.2.5 World cancer burden**

**Incidence**

*Incidence* is the number of new cases arising in a given period in a specified population. Often given as an absolute number of cases per year or as a standardized rate per 100,000.

*Age-standardized rate (ASR).* A rate is the number of new cases or deaths per 100,000 persons per year. An age-standardized rate is the rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of cancer.

The world standard population used in this report is as proposed by Segi.

Cancer is one of the leading causes of disease worldwide. An estimated 14.1 million new cancer cases occurred in 2012. Lung, female breast, colorectal and stomach cancers
accounted for more than 40% of all cases diagnosed worldwide. Out of total 14.09 million new cancer cases lung cancer was the most common cancer in men (1.825 million cases, 16.7% of all new cases in men) and breast cancer was by far the most common cancer diagnosed in women (1.677 million cases, 25.2% of all new cases in women), following by other sites of cancer, as colorectum 1.36 million, prostate 1.11 million, stomach 0.95 million, liver 0.78 million, cervix 0.53 million, esophagus 0.46 million.

**Mortality**

*Mortality* is the number of deaths occurring in a given period in a specified population. Often given as an absolute number of deaths per year or as a standardised rate per 100,000.

Cancer is the second leading cause of death worldwide (first are cardiovascular diseases), with *8.2 million deaths in 2012*.

More than half of all cancer deaths each year are due to lung (1.59 million), stomach (0.72 million), liver (0.74 million), colorectal (0.69 million) and female breast cancers (0.52 million).

**Prevalence**

The *prevalence* of a particular cancer is the number of persons in a defined population who have been diagnosed during a fixed time in the past with that type of cancer, and who are still alive at the end of a given year. It is usually given as a number, rate per 100,000 persons or a proportion.

Total of *32.5 million people diagnosed with cancer within the five years previously were alive at the end of 2012*. Most of them were women after their breast cancer diagnosis (6.2 million), men after their prostate cancer diagnosis (3.9 million), men and women after their colorectal cancer diagnosis (3.5 million), 1.9 million survivors after their lung cancer diagnosis and 1.5 million women after diagnosis of cervical cancer and similar number of people with stomach cancer (1.5 million). Relatively low was surviving in patients with liver cancer (0.63 million) and esophagus (0.46 million).

**Healthy Years of Life Lost**

*Healthy life years lost* (or *Disability Adjusted Life Years*, DALYs) are the sum of life years lost to premature mortality (deaths before the age of 80 years for males and 82.5 for females) and the years lived with disability, given as a number or as a standardized rate per 100,000.

An estimated 169.3 million years of healthy life were lost globally because of cancer in 2008. Lung (24.48 milion years lost), female breast (15.12 million), liver (15.49 million), stomach (14.2 million) and colorectal (12.25 million) cancers were the main contributors in most regions of the world, explaining 18% - 50% of the total healthy years lost.

2.2.6 **Cancer incidence, mortality and prevalence worldwide, international comparisons**

According to GLOBOCAN (excluding non-melanoma skin cancer) there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide.

In the less developed regions 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred. *Male incidence rates* vary almost five-fold across the different regions of the world, with rates ranging from 79 per 100,000 in Western Africa to 365 per 100,000 in Australia/New
Zealand (with high rates of prostate cancer representing a significant driver of the latter). The overall age standardized cancer incidence rate (ASRs World) is almost 25% higher in men than in women, with rates of 205 and 165 per 100,000, respectively. There is less variation in female incidence rates (almost three-fold) with rates ranging from 103 per 100,000 in South-Central Asia to 295 per 100,000 in Northern America. In terms of mortality, there is less regional variability than for incidence, the rates being 15% higher in more developed than in less developed regions in men, and 8% higher in women. In men, the rates are highest in Central and Eastern Europe (173 per 100,000) and lowest in Western Africa (69). In contrast, the highest rates in women are in Melanesia (119) and Eastern Africa (111), and the lowest in Central America (72) and South-Central Asia (65).

Cancer worldwide by organ site and international comparisons

WHO estimates 2012 of cancer worldwide by organ sites showing their ranking - numbers and rates, total and according to gender, as well as international comparisons illustrate marked differences in disease burden and geographic distribution.

Lung cancer - has been the most common cancer in the world for several decades. There are estimated to be 1.8 million new cases in 2012 (12.9% of the total), 58% of which occurred in the less developed regions. The disease remains as the most common cancer in men worldwide (1.2 million, 16.7% of the total) with the highest estimated age-standardized incidence rates in Central and Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000).

In women, the incidence rates are generally lower and the geographical pattern is a little different, mainly reflecting different historical exposure to tobacco smoking. Thus the highest estimated rates are in Northern America (33.8) and Northern Europe (23.7) with a relatively high rate in Eastern Asia (19.2). Lung cancer is the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total). Because of its high fatality (the overall ratio of mortality to incidence is 0.87) and the relative lack of variability in survival in different world regions, the geographical patterns in mortality closely follow those in incidence.

Breast cancer - is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers). It is the most common cancer in women both in more and less developed regions with slightly more cases in less developed (883,000 cases) than in more developed (794,000) regions. Incidence rates vary nearly four-fold across the world regions, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 96 per 100,000 in Western Europe. Breast cancer ranks as the fifth cause of death from cancer overall (522,000 deaths) and while it is the most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of total), it is now the second cause of cancer death in more developed regions (198,000 deaths, 15.4%) after lung cancer. The range in mortality rates between world regions is less than that for incidence because of the more favorable survival of breast cancer in developed regions with high-incidence. The rates were ranging from 6 per 100,000 in Eastern Asia to 20 per 100,000 in Western Africa.

Colorectal cancer - is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide. Almost 55% of the cases occur in more developed regions. There is wide geographical variation in incidence across the world and the geographical patterns are very similar.
in men and women: incidence rates vary ten-fold in both sexes worldwide, the highest estimated rates being in Australia and New Zealand (ASR 44.8 and 32.2 per 100,000 in men and women respectively).

Mortality is lower (694,000 deaths, 8.5% of the total) with more deaths (52%) in the less developed regions of the world, reflecting a poorer survival in these regions. There is less variability in mortality rates worldwide (six-fold in men, four-fold in women), with the highest estimated mortality rates in both sexes in Central and Eastern Europe (20.3 per 100,000 for men, 11.7 per 100,000 for women).

**Prostate cancer** - is the fourth common cancer worldwide and the second most common cancer in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions. Prostate cancer incidence varies more than 25-fold worldwide; the rates are highest in Australia/New Zealand and Northern America (ASR 111.6 and 97.2 per 100,000, respectively), and in Western and Northern Europe, because the practice of prostate specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions. Incidence rates are also relatively high in certain less developed regions such as the Caribbean (79.8), Southern Africa (61.8) and South America (60.1), but remain low in Asian populations. With an estimated 307,000 deaths in 2012, prostate cancer is the fifth leading cause of death from cancer in men (6.6% of the total men deaths). Because PSA testing has a much greater effect on incidence than on mortality, there is less variation in mortality rates worldwide (ten-fold from approximately 3 to 30 per 100,000) than is observed for incidence, with the number of deaths from prostate cancer larger in less developed than in more developed regions (165,000 and 142,000, respectively). Mortality rates are generally high in predominantly black populations (Caribbean, 29 per 100,000 and sub-Saharan Africa, ASRs 19-24 per 100,000), very low in Asia and intermediate in the Americas and Oceania.

**Cervical cancer** - is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. As with liver cancer, a large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. High-risk regions, with estimated ASRs over 30 per 100,000, include Eastern Africa (42.7), Melanesia (33.3), Southern (31.5) and Middle (30.6) Africa. Cervical cancer remains the most common cancer in women in Eastern and Middle Africa. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions. Mortality varies 18-fold between the different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Middle (22.2) and Eastern (27.6) Africa.

**Liver cancer** - is largely a problem of the less developed regions where 83% (50% in China alone) of the estimated 782,000 new cancer cases worldwide occurred in 2012. It is the fifth most common cancer in men (554,000 cases, 7.5% of the total) and the ninth in women (228,000 cases, 3.4%). In men, the regions of high incidence are Eastern and South-Eastern Asia (ASRs 31.9 and 22.2 respectively). Intermediate rates occur in Southern Europe (9.5) and Northern America (9.3). In women, the rates are generally much lower, the highest being in Eastern Asia and Western Africa (10.2 and 8.1 respectively). Liver cancer is the second most common cause of death from cancer worldwide,
estimated to be responsible for nearly 746,000 deaths in 2012 (9.1% of the total). The prognosis for liver cancer is very poor (overall ratio of mortality to incidence of 0.95), and as such the geographical patterns in incidence and mortality are similar.

**Stomach cancer** - almost one million new cases of stomach cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total), making it the fifth most common malignancy in the world, after cancers of the lung, breast, colorectum and prostate. This represents a substantive change since the very first estimates in 1975 when stomach cancer was the most common neoplasm. More than 70% of cases (677,000 cases) occur in developing countries (456,000 in men, 221,000 in women), and half the world total cases occurs in Eastern Asia (mainly in China). Age-standardized incidence rates are about twice as high in men as in women, ranging from 3.3 in Western Africa to 35.4 in Eastern Asia for men, and from 2.6 in Western Africa to 13.8 in Eastern Asia for women. Stomach cancer is the third leading cause of cancer death in both sexes worldwide (723,000 deaths, 8.8% of the total). The highest estimated mortality rates are in Eastern Asia (24 per 100,000 in men, 9.8 per 100,000 in women) and high mortality rates are also present in both sexes in Central and Eastern Europe, and in Central and South America.

**Esophageal cancer** - is the eighth most common cancer worldwide, with an estimated 456,000 new cases in 2012 (3.2% of the total), and the sixth most common cause of death from cancer with an estimated 400,000 deaths (4.9% of the total).

Around 80% of the cases worldwide occur in less developed regions. Esophageal cancer incidence rates worldwide in men are more than double those in women (male:female ratio 2.4:1). In both sexes there are more than 20-fold differences in incidence between the different regions of the world, with rates ranging from 0.8 per 100,000 in Western Africa to 17.0 per 100,000 in Eastern Asia in men, and 0.2 per 100,000 in Micronesia/Polynesia to 7.8 per 100,000 in Eastern Africa in women. Cancer of the esophagus has a very poor survival (overall ratio of mortality to incidence of 0.88), and the esophageal cancer mortality closely follows the geographical patterns for incidence, with the highest mortality rates occurring in Eastern Asia (14.1 per 100,000) and Southern Africa (12.8) in men and in Eastern (7.3) and Southern Africa (6.2) in women.

**World cancer trends**

Approximately 44% of cancer cases and 53% of cancer deaths occur in countries at a low or medium level of the Human Development Index (HDI).

**Human Development Index (HDI)** is a composite index of three dimensions of human development: - life expectancy (based on life expectancy at birth); - educational attainment (based on a combination of adult literacy rate and primary to tertiary education enrollment rates) and - income (based on GDP per capita adjusted for purchasing-power parity (PPP US$)). Countries were grouped into four levels of HDI according to the United Nations Development Program estimates for 2012: very high HDI, high HDI, medium HDI and low HDI.

As low HDI countries become more developed through rapid societal and economic changes, they are likely to become “westernized”. As such, the pattern of cancer incidence is likely to follow that seen in high HDI settings, with likely declines in cervix uteri and stomach cancer incidence rates, alongside increasing incidence rates of female breast, prostate and colorectal cancers. This “westernization” effect is a result of reductions in infection-related cancers, outweighed by an increasing burden of cancers more associated with reproductive, dietary and hormonal risk factors.
**Projections to 2030**

If recent trends in major cancers are seen globally in the future, the burden of cancer will increase to 23.6 million new cases each year by 2030. This represents an increase of 68% compared with 2012 (66% in low and medium HDI countries and 56% in high and very high HDI countries).

**2.2.7 Prevention of cancer**

Knowledge about the causes of cancer, and interventions to prevent and manage the disease is extensive. Cancer can be reduced and controlled by implementing evidence-based strategies for cancer prevention, early detection of cancer and management of patients with cancer. Many cancers have a high chance of cure if detected early and treated adequately.

**Primary prevention** of cancer aims at elimination or reduction of the impact of risk factors, so that cancer risk would be reduced or eliminated in populations and disease occurrence prevented. This being main domain of epidemiology.

**Secondary prevention** is focused on early detection of neoplastic process, its markers, precursor lesions or its signs, so as to prevent manifestation or reduce the morbid consequence of overt disease - cancer screening, highly effective in some cancer sites, and early diagnostics.

If clinically evident cancer ensues despite the above primary and secondary prevention strategies, there is a tertiary level of prevention - domain of clinical medicine.

**Tertiary prevention** concerns itself with the improvement in duration and quality of patient survival by reducing the risk of unfavorable clinical outcomes, involving palliative care.

**Primary prevention**

**Modifying and avoiding risk factors**

More than 30% of cancer deaths could be prevented by modifying or avoiding key risk factors, including:

- tobacco use
- being overweight or obese
- unhealthy diet with low fruit and vegetable intake
- lack of physical activity
- alcohol use
- sexually transmitted HPV-infection
- urban air pollution
- indoor smoke from household use of solid fuels.

**Tobacco use** is the single most important risk factor for cancer causing about 22% of global cancer deaths and about 71% of global lung cancer deaths. In many low-income countries, up to 20% of cancer deaths are due to infection by HBV and HPV.

**Prevention strategies**

- Increase avoidance of the risk factors listed above.
- Vaccinate against human papilloma virus (HPV) and hepatitis B virus (HBV).
- Control occupational hazards.
- Reduce exposure to sunlight.
Secondary prevention of cancer

Early detection
Cancer mortality can be reduced if cases are detected and treated early. There are two components of early detection efforts:

Screening
Screening is defined as the systematic application of a test in an asymptomatic population. It aims to identify individuals with abnormalities suggestive of a specific cancer or pre-cancer and refer them promptly for diagnosis and treatment. Screening programmes are especially effective for frequent cancer types for which a cost-effective, affordable, acceptable and accessible screening test is available to the majority of the population at risk.

Examples of screening methods are:
- visual inspection with acetic acid (VIA) for cervical cancer in low-resource settings;
- PAP test for cervical cancer in middle- and high-income settings;
- mammography screening for breast cancer in high-income settings.

Early diagnosis
The awareness of early signs and symptoms (for cancer types such as cervical, breast colorectal and oral) in order to get them diagnosed and treated early before the disease becomes advanced. Early diagnosis programs are particularly relevant in low-resource settings where the majority of patients are diagnosed in very late stages and where there is no screening.

Tertiary prevention of cancer

Treatment
Cancer treatment requires a careful selection of one or more intervention, such as surgery, radiotherapy, and chemotherapy. The goal is to cure the disease or considerably prolong life while improving the patient's quality of life. Cancer diagnosis and treatment is complemented by psychological support.

Treatment of early detectable cancers
Some of the most common cancer types, such as breast cancer, cervical cancer, oral cancer and colorectal cancer have higher cure rates when detected early and treated according to best practices.

Treatment of other cancers with potential for cure
Some cancer types, even though disseminated, such as leukemias and lymphomas in children, and testicular seminoma, have high cure rates if appropriate treatment is provided.

Palliative care
Palliative care is treatment to relieve, rather than cure, symptoms caused by cancer. Palliative care can help people live more comfortably; it is an urgent humanitarian need for people worldwide with cancer and other chronic fatal diseases. It is particularly needed in places with a high proportion of patients in advanced stages where there is little chance of cure.

Relief from physical, psychosocial and spiritual problems can be achieved in over 90% of advanced cancer patients through palliative care.

Palliative care strategies
Effective public health strategies, comprising of community- and home-based care are essential to provide pain relief and palliative care for patients and their families in low-resource settings.
Improved access to oral morphine is mandatory for the treatment of moderate to severe cancer pain, suffered by over 80% of cancer patients in terminal phase.

**WHO response**

In 2013, WHO launched the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2030 aiming to reduce by 25% premature mortality from cancer, cardiovascular diseases, diabetes and chronic respiratory diseases. WHO and the International Agency for Research on Cancer (IARC), the specialized cancer research agency of WHO, collaborate with other United Nations organizations and partners to:

- increase political commitment for cancer prevention and control;
- coordinate and conduct research on the causes of human cancer and the mechanisms of carcinogenesis;
- develop scientific strategies for cancer prevention and control;
- generate new knowledge, and disseminate existing knowledge to facilitate the delivery of evidence-based approaches to cancer control;
- develop standards and tools to guide the planning and implementation of interventions for prevention, early detection, treatment and care;
- facilitate broad networks of cancer control partners and experts at global, regional and national levels;
- strengthen health systems at national and local levels to deliver cure and care for cancer patients; and
- provide technical assistance for rapid, effective transfer of best practice interventions to developing countries.

**References:**

2.3 EPIDEMIOLOGY OF CHRONIC RESPIRATORY DISEASES

Hundreds millions of people suffer every day from chronic respiratory diseases. These very heterogeneous respiratory diseases include group of diseases of low respiratory airways and other structures of the lung, like chronic obstructive bronchopulmonary diseases with common characteristic of obstructive ventilation failure, diffuse parenchymatic lung diseases (interstitial inflammatory diseases, lung fibrosis) associated with inhalation of inorganic dust (pneumoconiosis), organic dust or unknown etiology (sarcoidosis) and very common allergic diseases of upper respiratory tract - allergic rhinitis and sinusitis.

Among chronic obstructive bronchopulmonary diseases most common and severe are chronic obstructive pulmonary disease (COPD) and asthma. COPD must be differentiating from asthma, but they are partially overlapping conditions that share some risk factors and clinical features. Both chronic diseases are major causes of illnesses, deaths and the use of health care resources causing heavy health and economic burdens worldwide with profound impacts on the quality of life for patients. The prevalence and burden of both chronic pulmonary diseases are projected to increase in the coming decades due to continued exposure to risk factors and the changing age structure of the world’s population (with more people living longer and therefore expressing the long-term effects of exposure to risk factors).

2.3.1 Chronic obstructive pulmonary disease

COPD affects approximately 210 million people worldwide and accounts for several million premature deaths per year worldwide. COPD is a major public health problem in subjects over 40 years of age, affecting more men than women, although rates in women are increasing.

In USA in 2002 an estimated 24 million adults had COPD. In the UK it is thought there are more than 3 million people living with the disease, of which only about 900,000 have been diagnosed and about 25,000 of them died per year. This is because many people who develop symptoms of COPD do not get medical help because they often dismiss their symptoms as a “smoker’s cough”.

The disease causes approximately more than 3 million deaths annually, and the number is projected to increase. COPD was the fifth cause of death in 2002 and it is projected to be the fourth place in the rank projected to 2030 worldwide.

There were several different definitions of COPD depending on accurate diagnosis. Small differences in the definition can have large effects on the estimates of COPD in the population. Global Initiative for Chronic Obstructive Lung Disease (GOLD) report classified COPD as a disease state characterized by persistent airflow limitation that is usually progressive and not fully reversible. The airflow limitation is due to inflammatory response of the lungs to noxious particles or gases in peripheral airways and lung parenchyma.

The American Thoracic Society (ATS) defined COPD as a disease state characterized by the presence of airflow limitation due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.

The European Respiratory Society (ERS) defined COPD as reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment.
Many previous definitions of COPD have emphasized two forms of COPD “emphysema” and “chronic bronchitis,” not including them in the definition used in current or earlier GOLD reports. However, most people have a combination of both conditions.

**Chronic bronchitis** is an inflammation of the lining of bronchial tubes. The main symptom is a long-term cough at least three months a year for two consecutive years. Chronic cough with sputum production may precede or follow the development of airflow limitation and may be associated with development and/or acceleration of fixed airflow limitation.

**Emphysema** occurs when the air sacs (alveoli) at the end of the smallest air passages (bronchioles) in the lungs are gradually destroyed, leading to destruction of the gas exchanging surfaces of the lung.

Emphysema and chronic bronchitis make up COPD, with three main pathophysiological components (inflammation, airflow limitation not fully reversible, gradual loss of lung function over time), which represent the major pathophysiological events leading to the symptoms of COPD. Signs of COPD often occur after significant lung damage which usually rise slowly and worsen over time. Chronic inflammation causes structural changes, the walls of the airways thicken and more mucus is produced with narrowing of the small airways and decrease lung elastic recoil.

The main symptoms are progressive cough with sputum production (chronic bronchitis), dyspnea (difficult or labored breathing) with wheezing, especially during physical activities, chest tightness, fatigue and later unintended weight loss. People with COPD are also likely to experience episodes, during exacerbations their symptoms become worse and persist for days or longer. Patients with COPD are susceptible to various respiratory infections, such as cold, flu and pneumonia.

These *exacerbations and comorbidities* contribute to the overall severity of COPD in individual patients. *Complications* of COPD include higher occurrence of some respiratory infections, pulmonary hypertension, heart problems, lung cancer and depression. The annual flu vaccination and regular vaccination against pneumococcal infections can help prevent pneumonia, further damage of lung and difficult breathing. Smokers with chronic bronchitis have greater risk of developing lung cancer than do smokers who don’t have chronic bronchitis.

**COPD prevalence and mortality** vary across countries and across different groups within countries with still increasing rates in most of the world and will probably continue to rise in response to increases in smoking, particularly in women and adolescents.

Epidemiological studies carried out recently in Europe and North America have shown that the prevalence of COPD in adults in industrialized countries with documented obstructive ventilatory disorder was 4% - 20% in adults over 40 years of age, more in men.

In population based surveys, COPD is often and best defined on the basis of spirometric assessment with post bronchodilator therapy when compared to patient – reported COPD (on symptoms). In meta-analysis using population based prevalence estimates during 1990-2004, it was shown that spirometric criteria revealed an almost twofold higher prevalence of COPD (9.2%) than reporting data (4.9%) respectively from general practitioners.

Global prevalence of COPD in 28 countries from meta-analysis showed pooled prevalence of 7.6%, the prevalence for chronic bronchitis alone was 6.4% and for emphysema alone 1.8%. Prevalence based on spirometry was 8.9%.

According to the projections, COPD will be *the fifth leading cause of DALYs lost* worldwide in 2020 behind ischemic heart disease (coronary heart disease), major depression, traffic accidents and cerebrovascular disease. This increment of global burden
of COPD reflects higher use of tobacco worldwide and the changing age structure of the populations in developing countries with the most dramatic rise of morbidity and mortality of COPD in Asian and African countries. In low and middle income countries exposure to risk factors for chronic respiratory diseases is high, including indoor air pollution, the use of solid biomass fuels and smoking.

Some of the risk factors for COPD are well known and include smoking, occupational exposures, air pollution, airway hyperresponsiveness, asthma, and certain genetic variations.

COPD is the result of cumulative exposures over decades. Often, the prevalence of COPD is directly related to the prevalence of tobacco smoking, although in many countries, outdoor, occupational and indoor air pollution – the latter resulting from the burning of wood and other biomass fuels – are major COPD risk factors.

Smoking is the main risk of COPD, it irritates and inflames the lungs, which results in scarring. The likelihood of developing COPD increases the more the person smokes and the longer he has been smoking. But some people smoke for years and never get COPD, such as less than 20% of smokers do not develop substantial airway obstruction.

Although COPD is attributed predominantly to tobacco smoke, occupational exposures are also suspected risk factors for COPD. Estimating the proportion of COPD attributable to occupation is thus an important public health need. Past occupational exposures significantly increased the likelihood of COPD independent of the effects of smoking. Given that one in five cases of COPD may be attributable to these exposures, like exposure to certain gases or fumes in the workplace and to heavy amounts of secondhand smoke and pollution, frequent use of cooking fire without proper ventilation.

In rare cases, nonsmokers who lack a protein alpha-1 antitrypsin can develop emphysema.

The chronic inflammatory response in the lungs in patient who developed COPD to inhaled cigarette smoke and other noxious particles (smoke from biomass fuels) may induce parenchymal tissue destruction (resulting in emphysema), and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These pathological changes lead to air trapping and progressive airflow limitation, and in turn to breathlessness and other characteristic symptoms of COPD.

COPD is commonly misdiagnosed, likewise, many persons who truly do have COPD are not diagnosed until the disease is far advanced and interventions are less effective. Pulmonary function tests are performed in those with symptoms of COPD and history of exposure to lung irritants (cigarette smoke). Airflow limitation is best measured by spirometry (blowing out as hard as possible into a spirometer), as this is the most widely available, reproducible test of lung function together with measurement of arterial blood gas analysis to measure the amounts of oxygen and carbon dioxide in the blood. Imaging tests of the lungs (x-rays, CT scans) can be helpful, but sometimes the lungs look normal even when a person has COPD.

COPD is classified into mild, moderate, severe and very severe disease measuring levels of FEV1 (forced expiratory volume in one second) and its ratio to the forced vital capacity (FVC). The main criterion for demonstration of airway obstruction in COPD is a FEV1/FVC ratio <70% due to reduced FEV1. This classification was found to correlate with pathologic findings and the prediction for death.

The new treatment management approach moves it towards individualized medicine – matching the patient's therapy more closely to his needs. Damage to lungs from COPD cannot be reversed, but treatment can help control symptoms and minimize further damage, focusing on minimizing risk factors and preventing exacerbations. With the exception of smoking-cessation programs for patients with early disease, home oxygen treatment for persistent hypoxemia, and lung-reduction surgery for selected
patients with emphysema, no treatment has been shown to reduce mortality. *Surgery* is only an option for a small number of people with COPD. *Antiinflammatory drugs* such as inhaled *corticosteroids* have little effect on the rate of decline of lung function but may reduce the frequency of exacerbations. Pulmonary *rehabilitation*, exercising, oxygen therapy and vaccination could improve life and contribute to relieve symptoms to keep COPD from getting worse. Newer measures, such as functional status or exercise capability, have emerged as important in determining the **prognosis** of COPD patients.

COPD is **treatable** but also **preventable** disease. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)** was implemented in 1998 with goals to increase awareness of the burden of COPD and to improve prevention and management of COPD through a concerted worldwide effort of people involved in health care and health care policy. Much has changed since the first GOLD Report in 2001, when **Global Strategy for the Diagnosis, Management, and Prevention of COPD** was published. At the time of the original report, improvement in both symptoms and health status was a GOLD treatment objective, but symptoms assessment did not have a direct relation to the choice of management.

A **new assessment system** was developed that draws together a measure of the impact of the patient’s symptoms and an assessment of the patient’s risk of having a serious adverse health event in the future. This has led to the construction of a new approach to management— one that matches assessment to treatment objectives. There are also simple **questionnaires** designed for use in routine daily clinical practice. **Identification, reduction and control of risk factors** of severe COPD with changes of lifestyle are important steps toward prevention and treatment of COPD. Measures against **smoking** should include quitting smoking, avoid places with second hand smoke or other types of air pollution which can irritate lungs. Smoking cessation could be provided by counseling, nicotine replacement and group programs. Successful quitting program needs encourage in several ways, including public policy, information and health education programs in media, at schools under the strategy proposed by health-care providers. The measures against **occupational exposures** should avoid potential occupational risk of COPD by elimination of professional exposures to dusts and chemicals in workplaces through surveillance and early case detection. Prevention of “*indoor and outdoor*” **air pollution** is decisive. If various solid fuels are used for cooking and heating adequate ventilation should be encouraged. Regulation of air quality free of fumes and dust should be a high priority with adequate legislative actions against outdoor pollution.

**Screening tests** are now available to detect the genetic defect that causes *alpha-1 antitrypsin* deficiency (A1AD) in parents and children especially in those with family history of COPD.

Resources aimed at prevention (smoking cessation), COPD education, early detection and better treatment of COPD will be of the most benefit in continuing efforts against this important cause of morbidity and mortality.

### 2.3.2 Asthma

**Asthma** is heterogeneous chronic inflammatory disorder with **reversible** air flow obstruction. Asthma is a public health problem not just for high-income countries; it occurs in all countries regardless of the level of development. It is is a global health problem affecting around 300 million individuals of all ages, ethnic groups and countries. Asthma is the most common non-communicable disease among children.

This disease has a relatively low case-fatality rate compared to other chronic diseases. Most asthma-related deaths are caused by failure to use appropriate medications
or to adhere the treatment. It is estimated that around 250,000 people die prematurely each year as a result of asthma, preferably in low- and lower-middle income countries.

Asthma is a major non-communicable disease characterized as a chronic disease of the air passages of the lungs which inflames and narrows them resulting in recurrent attacks of breathlessness and wheezing, mainly during night and early in morning which vary in severity and frequency from person to person. Symptoms may occur several times in a day or week in affected individuals, and for some people become worse during physical activity or at night. During an asthma attack, the lining of the bronchial tubes swell, causing the airways to narrow and reducing the flow of air into and out of the lungs. Recurrent asthma symptoms frequently cause sleeplessness, daytime fatigue, reduced activity levels and school and work absenteeism.

The fundamental causes of asthma are not completely understood. The strongest risk factors for developing asthma are combination of genetic predisposition with environmental exposure to inhaled substances and particles that may provoke allergic reactions or irritate the airways, such as indoor allergens (e.g. house dust mites in bedding, carpets and stuffed furniture, pollution and pet fur), outdoor allergens (pollens and moulds), tobacco smoke, chemical irritants in the workplace, air pollution. Other triggers can include cold air, extreme emotional arousal (anger or fear) and physical exercise. Even certain medications can trigger asthma, such as aspirin and other non-steroid anti-inflammatory drugs, and beta-blockers (treatment of high blood pressure, heart conditions, migraine). Urbanization has been associated with an increase in asthma, but the exact nature of this relationship is unclear.

Medication and appropriate management can control asthma and reduce the asthma burden. Asthma is under-diagnosed and under-treated. It creates substantial burden to individuals and families and often restricts individuals’ activities for a lifetime. Short-term medications are used to relieve symptoms and long-term medications daily (inhaled steroids) are needed to control the underlying inflammation, prevent symptoms and exacerbations and the progression of severe asthma. Inadequate access to medicines is one of the important reasons for the poor control of asthma in many settings.

Preventive avoiding of asthma triggers (stimuli that irritate and inflame the airways) can also reduce the severity of asthma. WHO recognizes that asthma is of major public health importance. The aim of its strategy is to reduce the disability and premature death related to asthma.

2.3.3 Bronchiectasis

Bronchiectasis is an abnormal widening of one or more airways. Normally, tiny glands in the lining of the airways make a small amount of mucus which keeps the airways moist and traps any dust and dirt in the inhaled air. Bronchiectasis (congenital or acquired) creates an abnormal widening of the airways with extra mucus, which are prone to infection. The main symptom of bronchiectasis is a cough which produces a lot of sputum, tiredness and wheeziness. A lung scan and other lung and sputum tests help to confirm the diagnosis.

The cause of bronchiectasis is often not clear. Some conditions that affect or damage airways can cause the disease, e.g. some inherited conditions (primary ciliary dyskinesia, cystic fibrosis), inhaled objects can block an airway, regurgitated acid from the stomach that is inhaled or any poisonous gases can damage airways and severe lung infections such as tuberculosis (TB), whooping cough, pneumonia or measles can damage the airways leading to bronchiectasis development.

Treatment includes regular physiotherapy, which helps coughing up and clearing the mucus, and courses of antibiotics. Surgery is occasionally needed.
2.3.4 Other chronic respiratory diseases

*Allergic rhinitis* is triggered by allergens, outdoor allergens, e.g. mould or trees, grass and weed pollens — it is often referred to as seasonal allergies, or “hay fever” or may also be triggered by indoor allergens found in the home, such as animal fur, indoor mould, or house dust mites. *Sinusitis* is an inflammation of the lining inside the sinuses which can be acute or chronic.

2.3.5 Prevention and control of chronic respiratory diseases

*Global Alliance against Chronic Respiratory Diseases* (GARD) contributes to WHO’s work to prevent and control chronic respiratory diseases. This alliance of national and international organizations focuses on the needs of low- and middle-income countries and vulnerable populations.

The objectives of the WHO strategy on chronic respiratory diseases are:

- Better surveillance to map the magnitude of chronic respiratory diseases and analyze their determinants with particular reference to poor and disadvantaged populations, and to monitor future trends.
- Primary prevention to reduce the level of exposure of individuals and populations to common risk factors, particularly tobacco, poor nutrition, frequent lower respiratory infections during childhood, and environmental air pollution (indoor, outdoor, and occupational exposure).
- Secondary and tertiary prevention to strengthen health care for people with chronic respiratory diseases by improving access to cost-effective interventions including medicines, upgrading standards and accessibility of care at different levels of the health care system.

References:

2.4 EPIDEMIOLOGY OF DIABETES

Diabetes mellitus is a heterogenic group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

In 2006 United Nations by the Resolution 61/225 recognized diabetes as a chronic, debilitating and costly disease associated with severe complications, which poses severe risks for families, Member States and the entire world. Diabetes is one of the most common non-communicable diseases and with rapid global increase has now reached epidemic intensity in most parts of the world.

2.4.1 Classification and pathophysiology of Diabetes mellitus

The classification of diabetes includes four clinical classes:

I. Type 1 diabetes mellitus
   A. Immune mediated
   B. Idiopathic
II. Type 2 diabetes mellitus
III. Other specific types of diabetes mellitus
   A. Genetic defects of ß-cell function
   B. Genetic defects in insulin action
   C. Diseases of the exocrine pancreas
   D. Endocrinopathies
   E. Drug or chemical induced
   F. Infections
   G. Uncommon forms of immune-mediated diabetes
   H. Other genetic syndromes sometimes associated with diabetes (Down syndrome, Klinefelter syndrome, Turner syndrome...)
IV. Gestational diabetes mellitus

The vast majority of cases of diabetes fall into the first two categories.

I. - type 1 diabetes mellitus (results from ß-cell destruction, usually leading to absolute insulin deficiency)
II. - type 2 diabetes mellitus (results from a progressive insulin secretory defect on the background of insulin resistance of tissues and may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance of tissue cells)
III. - other specific types of diabetes mellitus due to other causes, e.g., genetic defects in ß-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation)
IV. - gestational diabetes mellitus (GDM) - diabetes diagnosed during pregnancy

2.4.2 Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) accounts for 5-15 % of those with diabetes and it is the predominant form of the disease in younger age groups, mainly in children.
However, it can affect people of any age, with usually milder clinical manifestation when this type of diabetes is diagnosed at adult age. This form is called Latent Autoimmune Diabetes of Adults (LADA).

Type 1 diabetes typically results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Genetic and environmental factors are involved in the multifactorial nature of the disease.

The major genetic contribution comes from loci within the HLA (Human Leukocyte Antigens) complex, in particular HLA class II. Determining alleles can be either predisposing (HLA-DQ2, HLA-DQ8, HLA-DR3, HLA-DR4) or protective (HLA-DQ6, HLA-DR2), but the disease is probably due to a complex genetic factors and a polygenic or mixed model of inheritance in which a set of genes has an additive or interactive effect.

Risk of diabetes in offspring and sibling of a type 1 diabetic patient is about 5-10 %, which is 10-15 times higher than in general population. On the other hand only 12-15 % of type 1 diabetes occurs in families. Even that the estimate of the genetic effect in some countries was about 70% and genetic factors are thought to explain some of the geographic variability in T1DM occurrence, it cannot solely account for the disease development.

The increasing incidence of the disease with life-style changes in countries with low incidence of type 1 diabetes or in migrant populations suggests that environmental pressures are now able to trigger T1DM in subjects that previously would not have developed the disease during childhood. Among the possible environmental determinants are viral infections, increased height and weight development, increased maternal age at delivery, and some aspects of diet and toxins.

For decades viruses have been frequently implicated in the etiology of T1DM and this have been supported by seasonal variations in occurrence or the diagnosis of T1DM with lower incidence during summer period. Fetal or early postnatal infections caused by viruses, like congenital rubella infections, coxsackievirus B, cytomegalovirus, Epstein-Barr virus, reoviruses, and others have been related with development of T1DM. The mechanism of virus infection in the etiology of T1D is however still far from clear.

Some nutritional factors have been linked to T1DM and the early introduction of cow’s milk and short duration of breastfeeding have been reported to be associated with increased risk of type 1 DM. There are other dietary and toxic factors that may precipitate the expression of diabetes, such as meat, nitrosamines from smoked meat, gluten, gliadin, and others. However, so far, no specific dietary factor has been shown to be an unequivocal risk factor.

Epidemiological studies, mainly the Diabetes Mondiale study (DiaMond) and the Europe Diabetes study (EURODIAB) provide good evidence of increasing incidence of childhood onset type 1 diabetes in many countries.

Large variation in the incidence of T1DM exists between and within populations, being highest in Finland and Sardinia (Italy) and lowest in Venezuela and China. Countries with highest incidence rate for T1DM in children are shown in Figure 8.
High incidence, e.g. in Finland can be explained by a different genetic background as well as different distributions of risk factors, but part of the variability might be due to methodological problems (lack of data, imprecise extrapolation of data). The incidence has been increasing worldwide at an annual rate of approximately 3% and it seems that peaks around puberty. There is however only scarce data in the 15-19 year age-group. A total of 480 000 prevalent cases of T1DM in children population under 15 years was estimated in 2010, with 76 000 newly-diagnosed cases per year. Highest number of T1DM cases in childhood comes from the South-East Asian (SEA) (24%) and the European (EUR) regions (23%), and only some 6% come from Western Pacific (WP) region, despite it having the largest childhood population (Figure 9).
2.4.3 Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) accounts for about 85 to 95% of all diabetes in high-income countries and accounts for an even higher percentage in low- and middle-income countries. The disease is usually manifested after the age of 40 years, but there are increasing reports of worrying increase in younger age groups and even in children. Type 2 diabetes can remain asymptomatic, for many years and the diagnosis is often made from associated complications or incidentally through an abnormal blood or urine glucose test. Nevertheless, such patients with advanced diabetes mellitus are at increased risk of developing macrovascular and microvascular complications.

Most patients with T2DM are obese (with abdominal/central obesity) which itself can cause insulin resistance. The risk of the disease is positively associated to age, obesity (BMI over 30), lack of physical activity and insulin resistance. It is also more frequent in women with prior gestational diabetes mellitus, in subjects with hypertension, dyslipidemia and in different ethnic and racial groups. Particularly susceptible to the development of diabetes are American Indians, Pacific island communities, South Asians, Australian aborigines, African-Americans and Hispanics.

Strong genetic background of T2DM has been shown and familial clustering is even higher than in T1DM. Risk of developing T2DM was 3.5 times and 6.1 times higher in an offspring of one diabetic parent, or both diabetic patients, respectively, compared to general population in the Framingham Offspring Study. Genetics of T2DM are complex and polygenic, but major susceptibility genes have not yet been identified.

The rising prevalence of type 2 diabetes mellitus is associated with rapid cultural and social changes, ageing populations, increasing urbanization, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioral patterns.

Incidence, prevalence and time trends

According to estimates approximately 285 million people or 6.4% (prevalence), in the age group 20-79 had diabetes mellitus worldwide in 2010. About 70% of these people lived in low-and middle-income countries. Occurrence of diabetes mellitus worldwide increased, for comparison, in 1985 there were an estimated 30 million people with diabetes. Number of people with diabetes mellitus is expected to increase to some 438 million cases worldwide, with 7.7% prevalence by 2030, mostly of the adult population, with the largest increases in the regions in developing countries.

Figure 10. and Table 5. provide International Diabetes Federation’s data on prevalence of diabetes in seven WHO regions: Africa (AFR), Europe (EUR), Middle East and North Africa (MENA), North America and Caribbean (NAC), South and Central America (SACA), South-East Asia (SEA), and the Western Pacific (WP) in 2010 and 2030.

As age strongly influences prevalence of diabetes and world regions differ in age structure, the comparative prevalence (Figure 8. ,Table 5.) has been calculated by assuming that every country and region has the same age profile (adjusted to world population - standardized). The data presented are for types 1 and 2 diabetes mellitus combined, and only adults aged 20-79 years were considered because the majority of all people who have diabetes are adults.
Figure 10. Comparative prevalence (%) estimates of diabetes mellitus in 20-79 years old people by WHO regions, 2010 and 2030

Table 5. Regional estimates for diabetes in 20-79 age group in years 2010 and 2030

<table>
<thead>
<tr>
<th>Region</th>
<th>2010 Population (20-79)</th>
<th>No. of people with diabetes</th>
<th>Comparative diabetes prevalence</th>
<th>2030 Population (20-79)</th>
<th>No. of people with diabetes</th>
<th>Comparative diabetes prevalence</th>
<th>Increase in the no. of people with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>379 millions</td>
<td>12.1 millions</td>
<td>3.8%</td>
<td>653 millions</td>
<td>23.9 millions</td>
<td>4.7%</td>
<td>98.1%</td>
</tr>
<tr>
<td>EUR</td>
<td>646 millions</td>
<td>55.2 millions</td>
<td>6.9%</td>
<td>659 millions</td>
<td>66.2 millions</td>
<td>8.1%</td>
<td>20.0%</td>
</tr>
<tr>
<td>MENA</td>
<td>344 millions</td>
<td>26.6 millions</td>
<td>9.3%</td>
<td>533 millions</td>
<td>51.7 millions</td>
<td>10.8%</td>
<td>93.9%</td>
</tr>
<tr>
<td>NAC</td>
<td>320 millions</td>
<td>37.4 millions</td>
<td>10.2%</td>
<td>390 millions</td>
<td>53.2 millions</td>
<td>12.1%</td>
<td>42.4%</td>
</tr>
<tr>
<td>SMCA</td>
<td>287 millions</td>
<td>18.0 millions</td>
<td>6.6%</td>
<td>382 millions</td>
<td>29.6 millions</td>
<td>7.8%</td>
<td>65.1%</td>
</tr>
<tr>
<td>SEA</td>
<td>838 millions</td>
<td>58.7 millions</td>
<td>7.6%</td>
<td>1,200 millions</td>
<td>101.0 millions</td>
<td>9.1%</td>
<td>72.1%</td>
</tr>
<tr>
<td>WP</td>
<td>1,531 millions</td>
<td>76.7 millions</td>
<td>4.7%</td>
<td>1,772 millions</td>
<td>112.8 millions</td>
<td>5.7%</td>
<td>47.0%</td>
</tr>
<tr>
<td>Total</td>
<td>4,345 millions</td>
<td>284.6 millions</td>
<td>6.4%</td>
<td>5,509 millions</td>
<td>438.4 millions</td>
<td>7.7%</td>
<td>54.0%</td>
</tr>
</tbody>
</table>


However, in terms of absolute numbers (Table 5.), the Western Pacific Region (that includes China) with 77 million diabetes cases and the South-East Asian Region (that includes India) with 59 million cases had the largest number of people with diabetes in 2010, even that the comparative standardized prevalence rate (adjusted to the world population) of 4.7% for the Western Pacific Region and 7.6% for the South-East Asian
Region were lower than 9.3% for the Middle East and North African Region, and 10.2% in the North America and Caribbean Region.

Diabetes incidence and prevalence increases with age. In most countries the greatest number of people with diabetes is in the 40-59 year age group, with exception of Europe and North America and Caribbean Regions where greatest number of diabetics is in the 60-79 years age group. Epidemiological studies have shown that T2DM prevalence is rising even in younger age groups and even in children. T2DM now accounts for more new cases of diabetes in children and adolescents in Japan than T1DM and for 30% of new adolescent patients in some parts of the USA.

Top ten countries of the world with highest prevalence of diabetes are shown in the Figure 11.

*Figure 11. Top 10 countries´ prevalence of diabetes* in 20 -79 age group in 2010 and 2030

Little difference in the number of people with diabetes exists by gender. Large variability in type 2 diabetes mellitus prevalence however exists even within the same or similar ethnic groups, when living under different conditions (Figure 12.). Higher rates of type 2 diabetes are usually typical for migrant or urbanized populations with a greater degree of lifestyle change and the lowest rates in rural communities.
The incidence has been increasing worldwide at an annual rate of approximately 3% and it seems that peaks around puberty. There is however only scarce data in the 15-19 year age-group. A total of 480 000 prevalent cases of T1DM in children population under 15 years was estimated in 2010, with 76 000 newly-diagnosed cases per year. Highest number of T1DM cases in childhood comes from the South-East Asian (SEA) (24%) and the European (EUR) regions (23%), and only some 6% come from Western Pacific (WP) region, despite it having the largest childhood population (Figure 12).

**Mortality and complications of diabetes mellitus**

Diabetes is the *fourth or fifth* leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many low- and middle-income countries. The estimates of diabetes-related mortality show that the number of deaths is considerable and of a similar or greater magnitude to that caused by several infectious diseases. Diabetes related complications – both *microvascular* (neuropathy, nephropathy and retinopathy) and *macrovascular* (cardiovascular disease, stroke and peripheral vascular disease) – are a significant cause of increased morbidity and mortality among people with diabetes.

DCCT (Diabetes Control and Complication Trial) and UKPDS (United Kingdom Prospective Diabetes Study) studies have shown both in type 1 and type 2 diabetic patients that decreasing hyperglycemia can reduce microvascular complications and even that there was no such clear significant effect on macrovascular complications. However, prolonged follow-up of both studies have noted significant reduction of macrovascular complications in intensively treated patients.

High prevalence of the complications has been found in diabetic patients worldwide (Figure 13).
Cardiovascular disease is the major cause of death in diabetes, accounting in most populations for 50% or more of all death in people with diabetes. The risk for cardiovascular disease mortality is 2 to 4 times higher in diabetic patient than in people without diabetes. In cardiovascular diseases prevention, diabetes is considered as a risk equivalent of ischemic heart disease.

Diabetic retinopathy is the most common microvascular complication of diabetes and is a leading cause of blindness and visual disability. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy 71% patients with type 1 diabetes and 39% with type 2 diabetes without insulin therapy suffered on retinopathy. About 2% of all people who have had diabetes for 15 years become blind, while about 10% develop a severe visual impairment.

Diabetic nephropathy has now become the single most common cause of end stage renal disease in developed countries. Cumulative incidence after 40 years of D1TM is around 25%, similar is true for cumulative incidence after 20 years of T2DM duration. Diabetic nephropathy is often related to other microvascular and macrovascular complications of diabetes. In type 2 diabetes, the risk of developing cardiovascular disease is 2-3 times higher in someone with microalbuminuria compared to a person with normal albumin excretion.

Diabetic neuropathy can cause gastrointestinal, genitourinal, and cardiovascular disorders, impotence and other impairments and functional limitations. However the most common is peripheral neuropathy that can lead to sensory loss, muscle weakness
and pain with high risk for foot ulceration and lower-extremity amputation. Peripheral neuropathy affects 30-50% of diabetic patients.

Nontraumatic **Low-Extremity Amputations** are severe complication of diabetes. As many as 15% of diabetic patients will have such complication during their lifetime. People with diabetes carry a 10-20 times greater risk of amputation that in those without diabetes.

**Prevention of diabetes**

In last decades we saw a dramatic rise in the incidence of type 2 diabetes, but also rise in incidence of type 1 diabetes. However, at present type 1 diabetes cannot be prevented. Causal relationships of environmental triggers of type 1 diabetes (those without genetic factors) are still under investigation. On the other hand there is a lot of evidence that **lifestyle changes** (diet, body weight control and moderate physical activity) can help to prevent development of type 2 diabetes and thus most cases of type 2 diabetes are in theory preventable.

*A prevention of diabetes is performed at three mains levels:*

**Primary prevention** aims to prevent the development of risk factors and is therefore targeted to the whole population. Avoidance of obesity is the major target of primary prevention and it could be achieved at a population level by lifestyle interventions which lead to healthier eating and increased physical exercise.

**Secondary prevention** aims to prevent the development of diabetes and it targets individuals with borderline elevations of blood glucose (prediabetes) or other markers of risk. It is based on the earliest possible identification of disordered glucose metabolism (typically via population screening) and subsequent intervention. Several studies such as the Diabetes Prevention Program (DPP), Malmö study, Da Qing study, the Finnish Diabetes Prevention Study, and the Indian Diabetes Prevention Programme have demonstrated that lifestyle modification, based on modest weight loss and increased physical activity, have prevented or delayed progression of diabetes (30–60% reductions in type 2 diabetes incidence) in high risk individuals with impaired fasting glucose or impaired glucose tolerance.

**Tertiary prevention** is preventing the development of complications through early diagnosis and treatment of people with diabetes. Randomized controlled trials have shown compelling evidence that the microvascular complications of DM are reduced by tight glycaemic control. Intensive glucose-lowering exerts also favourable effect on macrovascular complications of DM, however only in patients with a short duration of T2DM, lower baseline HbA1c at randomization, and without a history of CVD.

**References:**


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