Peer reviewed article

Geriatric epidemiology: practical considerations when involving elderly subjects in studies

François R. Herrmann

Department of Rehabilitation and Geriatrics, Hôpitaux Universitaires de Genève

Summary

Geriatric epidemiology deals with the application of epidemiological techniques to the study of elderly persons. It is neither a simple replication of studies carried out in younger adults transposed to another collective nor a departure from basic principles. It is rather the integration of known methods, which should be taken systematically into account during their application to geriatric populations, in order to circumvent the specific problems involved in the study of this growing part of the population.

This paper aims to provide an overview of the practical implications of the epidemiological study of the elderly. It is divided in two parts. A concise description of the demographic context underlining the topic relevance is followed by a discussion of the methodological aspects. It attempts to remind potential investigators of some important issues raised while studying older persons and also provide clinicians with criteria for assessing the quality of papers they read on this topic.

Key words: geriatric; epidemiology; methods

Introduction

Tacitis senescimus annis
Ovide, Fastes, VI, 771.

Demography, like epidemiology, is interested in the study of populations and the two disciplines share concepts and exchange data. Indeed, population statistics collected by government services are essential to determine the denominators used in prevalence and incidence calculations carried out by epidemiologists during population surveys. The results of these computations can then be reused to estimate population health indicators, such as disease-free life expectancy. Finally, numerical evaluations of elderly populations by demographers stress its importance as a subject of interest for public health.

Demographic aspects

General

In 1860, the year of the first federal census, Switzerland had 2.5 million inhabitants including 5.1% persons aged 65 years and over (65+), 0.1% aged 85 years and over (85+) and 10 centenarians. One century later, in 1960, the resident population had more than doubled, reaching 5.4 million with respectively 10.2% of citizen aged 65+, 0.5% aged 85+ and 23 centenarians. In the 2000 census, the population exceeded 7.2 million, with 15.4% 65+, 2.0% 85+ and 796 centenarians.[1] The population pyramid is thus transformed into a "haystack", and tends to become more rectangular, especially for women. The Federal Office of Statistics (OFS) has developed several scenarios for the future evolution of the total population [1]. In 2060, the overall Swiss population should range between 5 and 8.5 million people. However, whatever the scenario, from 2040 onwards one quarter of the resident population of the country will be aged 65+ unless an unforeseeable catastrophe occurs. In the event of a continuing fall in the birth rate, the elderly population could rise to 26%, whereas in the opposite case it will stabilize at around 23%. The other developed countries follow similar trends. In developing countries, population ageing is occurring over an even shorter period than that observed in the developed countries. Thus this fast structural change leaves little time to adapt to the new situation.

No financial support declared.

1 Data communicated by the Federal Office of Statistics, provisional results of the 2000 census as of the 14th January 2003.

Demographic transition

The observed population ageing is explained by a phenomenon called the "demographic transition". It corresponds to the passage from a young population, characterized by a strong fertility and a high mortality rate, to an older population with low mortality and fertility rates [2, 3]. This transition is initiated by a marked reduction in death rates, especially of peri-natal and infant mortality, followed in time by a reduction in birth rate. This reduction in mortality results in an increase in life expectancy, whereas birth rate reduction involves an increase in the proportion of elderly subjects. Data from the Swiss Federal Office of Statistics (http://www.statistik.admin.ch/) shows that the decrease in mortality began around 1880 and stabilized in the 1970s, and that the reduction in fertility rates started about 1900 and reached a plateau around 1980. With the current fertility rate of 1.48 children per woman in reproductive age, the replacement of the Swiss population is not assured (2.1% corresponding to the threshold of stability), at least not without immigration.

Epidemiological transition

The demographic transition is accompanied and generated by another phenomenon called the "epidemiological transition", which is defined by a shift in the causes of death due to:

- the reduction of infectious causes, in particular epidemics, characterized by a short latency between the exposure and the fatal outcome
- the progressive increase in deaths due to degenerative diseases such as cardiovascular and neoplastic pathologies, which are characterized by a latency of several years between their onset and death [2–4].

This epidemiological transition has resulted not only in a rise in the prevalence of chronic diseases, but also in a notable increase in the number of centenarians [5].

Emergence of centenarians

Since the middle of the nineteenth century the total population of Switzerland and the proportion of older citizens aged 65+ has tripled, whilst the proportion aged 85+ has increased by a factor twenty.

A corollary to population ageing with good health care [6] is the increase in the number of centenarians and super-centenarians (people aged 110 years old or more) [7] and the observation of confirmed records of human longevity [8, 9]. Centenarians were so rare in the past that most national statistics grouped them together with the stratum of the 85+ [10]. Today they are becoming the subject of both retrospective [11] and prospective epidemiological studies [7, 11–16], whose objectives are to identify genetic factors associated with the avoidance or delay of the fatal outcome of the diseases usually associated with growing older, such as cognitive disorders, cardiovascular diseases or cancer.

To become a centenarian is no longer an exception. Nevertheless, centenarians form a very heterogeneous group of survivors. Selective pressure on individuals can be exerted differently according to the cohort they belong to. For example, it is a reasonable assumption that a particular gene constellation could be necessary to survive food restriction, two world wars and the 1918 influenza pandemic. However, tomorrow's centenarians will face other challenges. They will have to deal with other viruses (AIDS, SARS), prion diseases, food plethora, air pollution or various food contaminants. It is possible that these potentially harmful events could be counterbalanced by the acquisition of new knowledge on risk factors, by the adoption of preventive lifestyle or the discovery of new therapeutic agents.

Roots of geriatric epidemiology

Epidemiological reasoning is based on the postulates that diseases do not occur by chance only and that it is possible to identify aetiological or preventive factors by comparing groups of individuals [17]. Hippocrates (460–377 B.C.) already recognised that the origin of diseases could be attributed to external causes such as place of residence, quality of water, season or lifestyle [18]. Two millennia later, in the United Kingdom, Francis Bacon (1561–1626) in his "*History natural and experimental of life and death or of the prolongation of life*" proposed a study on the longevity of people in defined locations [19]. However it was John Graunt (1620–1674) who was the first to exploit routinely collected numerical data in the form of weekly reports of births and death by parish to describe disease distribution in London. Two centuries went by before William Farr (1807–1883) set up systematic, nationwide annual reports in England and Wales, enabling him to compare death rates among various population groups, thus laying down the foundations of descriptive epidemiology. The existence of these data made it possible for John Snow (1813–1858) to carry out one of the first studies of causal epidemiology during which he could confirm the assumption that the cholera epidemic which occurred in London in 1853–1854 was related to the source of the drinking water supply [17, 20].

In 1909, the word "geriatrics" was coined in New York, by Ignace Leon Nascher (1863–1944), a native Austrian, recognized by medical histo-rians as the father of the speciality, who published the first treatise on the care of old people in 1914 [21].

Initially epidemiology primarily devoted itself to the study of the epidemics caused by infectious diseases, the main cause of the high mortality that prevailed prior to the transition. Since the 1950's, however, epidemiology has gradually become interested in the study of chronic diseases using retrospective studies such as that of Doll and Hill in 1950, which established a strong suspicion of a causal link between smoking and bronchial carcinoma [22]. At the same time the first large scale prospective studies were initiated. For example, the Framingham Heart Study, established in 1949 [18], is still ongoing 50 years later, and now addressing geriatric topics [23, 24]. In 1954, the first major randomised clinical trial, involving nearly a million school children showed the effectiveness of the Salk vaccine against poliomyelitis, an infectious disease with chronic neurological consequences [17, 18].

Since the 1980's many prospective epidemiological studies have focused on the elderly. In the United States, the EPESE project *(Epidemiological Studies of the Elderly)*, is following four significant populations of old people [25–27], residents in East Boston *(East Boston Senior Health Project)* [28, 29], in New Haven *(Yale Health and Aging Project)* [30], in two sites in Iowa *(Iowa 65+ rural Health Study)* [31], and in Piedmont, North Carolina [32]. In Switzerland, the Basler study has followed a male cohort of retired workers from the pharmaceutical industry since the end of 1960 [33–35]. Recently, several prospective ongoing projects focused exclusively on centenarians [7, 11–16]. In 1991, a paper by Miettenen specifically mentions the epidemiology of ageing [36], and in 1992 the first textbook on this subject was published [37].

The number of publications indexed in the Medline database, using the medical subject headings "elderly" and "epidemiological study", confirm the growing interest in the topic. The number of indexed papers has reached more than 800 per year since the year 2000.

Geriatric epidemiology

Epidemiology, which is better characterized by its research tools than by a specific knowledge [38], is at the interface of several disciplines:

- clinical medicine for defining research questions, diseases, risk factors and the choice of case detection methods.
- medical genetics for identifying family risk factors.
- social sciences for targeting socio-economical risk factors.
- psychology for creating questionnaires and validation techniques.
- demography for gathering data, which are essential to determine the denominators used in calculations of prevalence and incidence.
- biostatistics for the calculation of confidence intervals, statistical tests, as well as the determination of statistical inferences.

Most epidemiological textbooks contain no methodological chapter on the specificities of studies in the elderly [17, 18, 39–41]. Only two handbooks cover the subject. "The Epidemiological Study of the Elderly" edited in 1992 by R. B. Wallace and R. F. Woolson [37], which is the most complete from a methodological stand point and "Epidemiology in Old Age" edited in 1996 by S. Ebrahim and A. Kalache [42], which is the only one to contain a chapter devoted to the fundamental principles of old age epidemiology [43]. However, information relating to methodology is scattered over the 800 pages of the two textbooks, which are organized in broad topics, and are therefore difficult to access for a clinician eager to write a study protocol involving elderly subjects.

Thus to describe the specificity of geriatric epidemiology, we will follow the structural logic of a research project, highlighting the pitfalls to avoid and proposing some straightforward solutions, while keeping in mind that the choice of the research question remains at the heart of any protocol.

Methodological aspects characteristic of geriatric epidemiology

Study design

The choice of the study design depends primarily on the research question. As observed by G. L. Burket the classification of research designs vary widely among textbooks and can be quite confusing. He proposed a taxonomy based on three axis, modified by Jenicek: the type of the research objective (exploratory, descriptive, or analytic), the time factor (retrospective, cross-sectional, or prospective) and the presence of intervention (observational or interventional) [40, 44]. In the following examples, we will mainly follow the time axis.

In *retrospective studies*, the patient's status is known with certainty and one seeks the exposure to the risk factor in the past. It is the most problematic design when dealing with elderly persons. Indeed, as memory impairment and dementia increase with age, the reliability of the information obtained by interview can be of doubtful validity. Two solutions make it possible to improve relia-

bility. The first consists in relying on written documents and the second in crosschecking the information provided by an informant who knows the subject well. In a review of 165,000 anaesthesias, data collection was based on anaesthesia protocols [45]. In another project, the spouse or a family member was systematically questioned to validate the information given by the subjects [46]. This procedure requires ad hoc logistics to obtain consent from the subjects and longer interviews, which in turn affects the budget.

Cross-sectional studies determine simultaneously potential risk factors and the disease status, for example ApoE genotyping and the presence of dementia [46]. They allow determination of the prevalence, which measures the proportion of a population suffering from a disease at a given moment.

Prospective cohort studies are the only ones that allow the incidence to be determined, that is to say the number of new cases of a condition in a given population over a fixed period. The exposure to risk factors is known with certainty at the beginning of the investigation and events of interest are recorded progressively [47, 48]. Thus, it is possible to evaluate in an *observational prospective cohort study*, the predictive value of a refrigerator containing less than three food items at the time of home visit on the risk of hospitalisation of its owner [49]. *Intervention studies*, can only be prospective, and imply an active role on the part of the investigator, such as prescribing different types of influenza vaccine [50], or Midazolam at the time of endoscopy [51]. Randomised clinical trials, a classical subtype of intervention studies, involving the elderly call for an increased vigilance in the monitoring of possible side effects.

Population selection

Three issues must be considered. Firstly, given that the rates of institutionalisation increase with advancing age, the exclusion of nursing home residents (20% of nonagenarians) in population studies, generates a selection bias [46, 52, 53]. It leads to the underestimation of the prevalence of diseases common among the elderly, notably incontinence and dementia. Conversely, studies limited to institutionalised or hospitalised populations concentrate on sicker subjects.

Secondly, population-based studies are more difficult to complete with the elderly. In particular the consent of the nursing home management is needed before gaining access to the residents and only then can the researcher try to obtain informed consent from the latter. Since cognitive impairment may be highly prevalent, the task at hand is further complicated by two elements. Firstly systematic assessment of cognitive status is necessary, even if this is not the study's main objective [54], and secondly the information provided by the elderly subject has a lower reliability, so that this must be cross-checked with a proxy, a further informant who knows the proband well. This means that both a greater amount of time must be devoted to the subject's interview and leads to a doubling in the number of persons to be interviewed thus increasing the overall study cost. However despite these problems, population-based studies involving elderly are available. [23, 46, 52, 53, 55–57].

Thirdly, economically favoured elderly tend to gather in privileged places (for example, Tessin in Switzerland, seaside resorts in England, Florida and California in the United States). Consequently, a study in these areas would not reflect the situation of the whole country, because the people who moved under more lenient skies are often in better health [43].

Criteria of inclusion and exclusion

Elderly persons are often excluded from surveys [57] and randomised control trials because of age limits fixed at 60, 65 or 75 years, this being particularly true for anti-cancer treatment. These age limits are justified by the fact that elderly patients are more fragile and develop side effects more easily, frequently present multiple co-morbidities for which they receive other treatments which could interfere with the substance under study, or because of the exponential increase in the prevalence of dementia with age, which renders informed consent virtually impossible. Thus, the results of such studies cannot be extrapolated directly to most elderly patients.

The selection of healthy subjects, without any condition other than the disease under investigation, will provide a more rigorous study from a scientific stand point, but can also generate significant selection bias, limiting the use of the results in everyday clinical practice. The typical geriatric patient attending a consultation seldom matches those of the original study, leaving the clinicians with few evidence-based data to decide what is best for their patients.

Sampling

Some advanced age strata are still relatively small in the population (although this might change in the next decades) and with increasing gender asymmetry with age, a random sampling will select only a minority of very old subjects, who will also have a weak probability of being of male sex. So, to obtain correct estimators in these age groups, randomised sampling stratified by age and gender is recommended. This will yield an equivalent number of subjects in each stratum. This kind of sampling implies the use of particular analysis techniques which integrate appropriate weighting factors for each strata [46, 52, 53].

Variables definition

Clinical or epidemiological definitions of certain geriatric diseases prevent one from categorizing the patients in a binary way, as "diseased" or "healthy". Erkinjuntti showed the significant variations in prevalence estimates of dementia (ranging from 3% to 30%) according to the disease clas-

sification used [58]. This lack of a "gold standard" complicates the realization of studies and their analysis by misclassifying the subjects. A local survey showed the low sensitivity of clinical criteria for vascular dementia after neuropathological validation [59].

On the one hand, the multiple diseases of the geriatric patient (4.7 diagnoses on average per patient at the Rehabilitation and Geriatrics department of Geneva University Hospital) require the collection of a large number of parameters to correctly define the studied population, which increases the cost of the study. On the other hand, there is an increase in conditions in which the scarcity of symptoms renders a clinical diagnosis, which would be obvious in a younger subject, such as a bronchopneumonia manifesting itself with confusion in the absence of both cough and temperature, more difficult. Fortunately, genetics and molecular epidemiology can identify markers like ApoE to obtain perfect cases classification [46, 60, 61].

Age itself is a key variable, because it can also be a confounder, when it is simultaneously associated with risk factors and the disease under study, as is frequently the case. The techniques used to control confounding effects are matching, standardization or adjustment. It is recommended that age be determined precisely and the use of categories for age avoided. Categories can always be defined using the detailed data. This remark is valid for any continuous variable.

Functional status is a key aspect of geriatric assessment, as it becomes a main reason for institutionalisation with advancing age. Several different validated evaluation scales are available such as Katz's ADL [62, 63], the Barthel's Index [64] or the Functional Independence Measure [65, 66]. In some studies the subject assesses his own functional status [67, 68], and may thus be expected to overestimate his true performance. However, a recent Swiss study comparing subjects' and proxies' assessments suggests that even cognitively impaired subjects are able, in certain instances, to give reliable information [69]. Despite this, when in doubt it is often preferable to rely on an informant or to perform a direct observation, which is more easily done in a hospital or a nursing home setting, to improve the quality of this variable. When different raters are involved, it becomes necessary to evaluate their inter-rater agreement.

The issue of pain, health or quality of life assessment, relying respectively on instruments like the visual analogue scale [70], the Short-Form Health Survey questionnaire (SF-36) [71] and Quality adjusted life year (Qualy), constitutes a true challenge with the cognitively impaired, particularly the severely demented [70].

Sample size and statistical power

Once the research question and the study design have been determined, the choice of statistical methods is straightforward. Depending on the desired precision of the results, the sample size computation can be established either from formulae, statistical tables, or using ad hoc software. This operation requires the knowledge of certain parameters (expected proportion of success, expected average and variance), which can be obtained from the literature, a pilot study or logical assumptions. If using figures from studies carried out on younger subjects, it should be remembered that the variance of several clinical and biological parameters increases with age. Certain individuals maintain normal values, whereas others have results outside normal limits. In the absence of a pilot study involving elderly subjects, it is thus necessary to increase the variance value obtained from the literature, which will result in a higher number of elderly subjects needing to be included in the protocol.

When planning the use of multivariate methods, the following empirical rule applies. It is necessary to count approximately 10 observations for each variable included in the model. However, when the outcome is binary, as in logistic or Cox's regression, the rule of 10 observations per independent variable applies to the lowest frequency observed [72, 73]. For example, only 20 variables could be studied simultaneously, if the prevalence of dementia amounts to 20% in a group of 1000 people (20% *1000/10 = 20).

Once the target number of patients is computed, it is necessary to determine the size of the real sample, namely to integrate the rate of probable participation, the proportion of lost to follow-up and the risk of death. It is known that with advancing age [74] the rate of participation decreases just as the probability of dying increases. Equation 1 shows the formula used to calculate the number of participants required.

Equation 1

Formula to estimate the number of subjects needed in a study (N_{Final}), after having carried out sample size calculation using usual statistical power analysis (N_{Power}). Death risk, refusal rate and drop out rate are expressed in percent.

$$N_{Final} = N_{Power} * (1 + \text{Death risk} + \text{Refusal rate} + \text{Drop out rate})$$

In the Swiss dementia study, 72 (3.3%) randomised subjects died between the point of selection and the investigators' attempt to contact them [46]. Needless to say, this kind of situation requires a tactful approach of the related families.

In the field

Informed consent can be more difficult to obtain from an elderly person, because of sensory impairments.

Deafness reduces the quality of oral communication, especially during telephone investigations, which are nevertheless possible to realize [75–77], but present a risk of selection bias, poorer people being more prone to dispense with the use of a telephone.

Visual impairment can prevent reading. Thus any explanations must be written in a comprehensible way and printed in contrasted and large fonts. The presence of cognitive impairment obliges one to obtain the consent of a guardian or other legal representative in addition to the subject's own informed consent. This requirement is already difficult to meet in a hospital setting, and almost impossible to satisfy in a population-based study. The ideal way to overcome this difficulty is to enrol cognitively intact subjects and obtain their approval before the possible onset of dementia. Simply obtaining the consent of a next of kin or another proxy is usually insufficient for approval by an ethical committee.

A patient who has previously given consent can later forget this decision. It has been known to happen for an investigator to be met by the police at a patient's home, because that elderly person could not remember why she was been "bothered". The subject should thus always be informed in writing first, and then contacted by telephone with a reminder of the appointment a short time before the visit. For security reasons, we recommend that investigators performing home visits carry proof of their official status, and elderly persons expecting the visit of an interviewer should check this identity document.

Data collection and quality control is a capital phase in the course of a study. As mentioned above, the access to a person of reference *(proxy)* or to written documents (to check the date of birth) will improve the quality of collected information.

Functional impairment

Walking impairment limits the capacity of old people to move to external facilities to be interviewed or examined. To maximize participation rates it is judicious to propose home visits to those with walking impairment, as well as an institutional external place to those who cannot tolerate an intrusion of their privacy or who fear for their safety.

Sensory or memory impairment can make certain evaluations difficult or even impossible. In addition, some old persons tire quickly and their attention weakens in the course of the interview. The investigator is then confronted with the following paradox. He should collect sufficient information to better describe the elderly population, whereas at the same time it is imperative that the instruments used be as short as possible. One logical alternative consists in splitting the interviews into two or three meetings, another factor which requires great flexibility on behalf of the investigators and raises the costs of a project [46, 52, 53].

Statistical aspects

The need for carrying out adjustments by age and gender is obvious due to the demographic asymmetry between genders. During data analysis, it is necessary to keep in mind that the high prevalence of many conditions (osteoarthritis, functional impairment, dementia, falls, etc.) implies that odd ratios calculated by logistic regression will not be equivalent to relative risks. Figure 1 indicates that the odds and the risks are identical for prevalence smaller than 10%, and that both parameters diverge quickly above a prevalence of 30%. The same relation is true when comparing odd ratios and relative risks. When the prevalence is high, it means that the odd ratios tend to overestimate the true relative risk.

Interpretation

While interpreting the results, it is necessary to integrate thoroughly all of the preceding re-

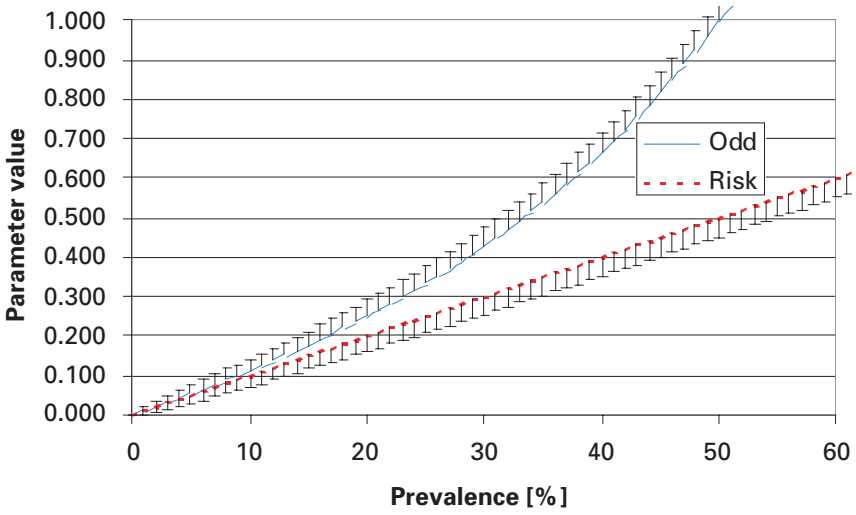

Figure 1
Relation between the odd (p / [1 – p]) and risk (p) according to prevalence showing the equality of both parameters below a prevalence of 10% and a statistically significant divergence above 30%. Value are shown with standard deviation for N = 100.

marks and to discuss cohort effects, period effects and effects directly related to age itself because these three parameters are narrowly dependent. To address this question precisely it is necessary to study various cohorts over several periods of time [78].

The elderly are, by definition, survivors who crossed the years while being exposed in a variable way to many risk factors. Thus, they constitute a very mixed group and the results highlighted in a study cannot automatically be generalized.

Conclusions

The ageing of a population is a gradual phenomenon that is accelerating and will be experienced by most nations with a few exceptions, such as Russia, during this century. It will necessitate a progressive reorganization of human societies, particularly of their health care and social security schemes [79–81], as Switzerland is currently attempting. Epidemiology, adapted to the geriatric field, gathers a set of descriptive and analytical tools that allow:

- the medical problems of the generations that preceded us to be quantified and enables us to define which of them will constitute priorities for preventive, curative and palliative health care policies.
- the calculation of health indicators that will allow the comparison of population health status across time and space.
- the evaluation of the impact of adaptative changes to the health care system and medical services.
- the identification of risk factors for chronic diseases, in particular the interactions between the environment and genetic characteristics, and thus to direct to a certain extent the activity of basic research laboratories and the pharmaceutical industry.
- the development of screening and prevention strategies.

Tomorrow's elderly have already been born. Their future diseases and needs might be quite different from those affecting today's older citizens. As Rosenmayr propounds in his proposals, a contemporary culture of ageing is emerging, which should be able to reconcile the paradox of frailty and the finality of human beings while defining new objectives and renewed ideals [82].

Acknowledgement: We are indebted to Mr. Bernard Grab for his thoughtful advice, to Mrs. Anne Scherrer for editorial assistance and to Mrs. Barbara Gotsch from the Swiss Federal Office of Statistics for providing us with the census data.

Correspondence:
PD Dr François R. Herrmann
Department of Rehabilitation and Geriatrics
Hôpitaux Universitaires de Genève
3, ch. de Pont-Bochet
CH-1226 Thônex
E-Mail: francois.herrmann@hcuge.ch

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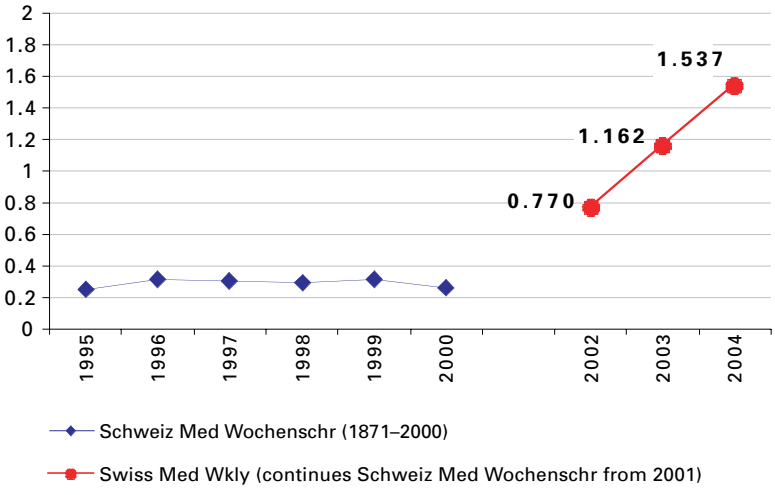

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