

UNDERSTANDING CHANGING RISK FACTOR ASSOCIATIONS WITH INCREASING AGE IN ADULTS

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ABSTRACT

With an increasingly older population, there is considerable interest in understanding the potential for risk factor interventions in order to prevent, postpone, or slow down the common diseases seen in older persons. However, it is often reported that the strength of association between risk factors and common disease outcomes decreases with increasing age. Actually, many different age-related patterns are observed. Understanding these patterns requires knowledge of issues related to the pathophysiology of aging, including age-related physiologic and metabolic alterations, detection and diagnosis of disease in the elderly, measurement of risk factors, sample selection, comorbidity, competing risks, selective survival, ceiling effects, and methods of analysis in aging populations.

INTRODUCTION

Striking changes in the age structure of the population continue to be seen in most economically developed countries, with the proportion of older persons increasing. Although decomposing the exact mix of reasons related to fertility and increased survival is complex, changes in life expectancy have been

dramatic. For example, in the United States between 1940 and 1995, life expectancy at birth increased by 21% for females and 19.2% for men (47). Much of the improvement in life expectancy during this period is due to increased survival at older ages. Men and women who reach age 65 in the United States can now expect to live 15.7 and 18.9 years more, respectively. Similarly, life expectancy at age 80 has increased to 8.9 years for women and 7.3 years for men.

Within the context of an aging population, epidemiologic attention has increasingly turned to the role of primary and secondary prevention in the elderly, with a focus on both longevity and quality-of-life issues (18, 28). Although the societal and clinical imperatives for such an approach are clear, the data supporting the role of prevention in the elderly are often met with some skepticism. Foremost among the reasons for this skepticism is the belief that there is a dominant pattern of decreasing strength of association between risk factors and outcomes with advancing age.

Is such a pattern commonly found? Because few published reports actually present age-specific data or explore the oldest age groups, it is difficult to arrive at any definitive statement about the relative frequency of various patterns. The data presented in Figure 1, although not intended to present a representative picture, illustrate that, in a number of studies with either cardiovascular outcomes or mortality from all causes, several different age-related patterns are found. The figure shows results taken from five published studies and two analyses of data from the Alameda County Study by one of the authors (GA Kaplan, unpublished observations). Note that where only an age range was specified, the midpoint of that range is plotted. The pattern of declining strength of association with increasing age is shown in Whisnant et al's analysis (61) of the association between current smoking and incidence of ischemic stroke. A similar, but shallower, decline is seen in data from the Framingham Heart Study relating hypertension to annual incidence of coronary heart disease (49). Increases in relative risks with increasing age are illustrated in three examples. In the Honolulu Heart Program, the association between systolic blood pressure in the top quartile versus lowest quartile (150 versus <122 mm Hg) and incidence of coronary heart disease was greater in those 65–74-years old than in those 51–59 (3). An age-related increase in the association between high levels of total serum cholesterol (6.7 mmol/liter versus lower levels) and mortality from coronary heart disease was also seen in the Charleston Heart Study (31). The association between prevalent diabetes and risk of coronary heart disease in women, but not men, was found to be higher among 65–74-year olds than in 55–64-year olds in the National Health and Nutrition Examination Survey (NHANES)-I Epidemiologic Follow-up Study (NHEFS) (34). Mixed patterns are also seen. In the Alameda County Study, both obesity (85th sex-specific

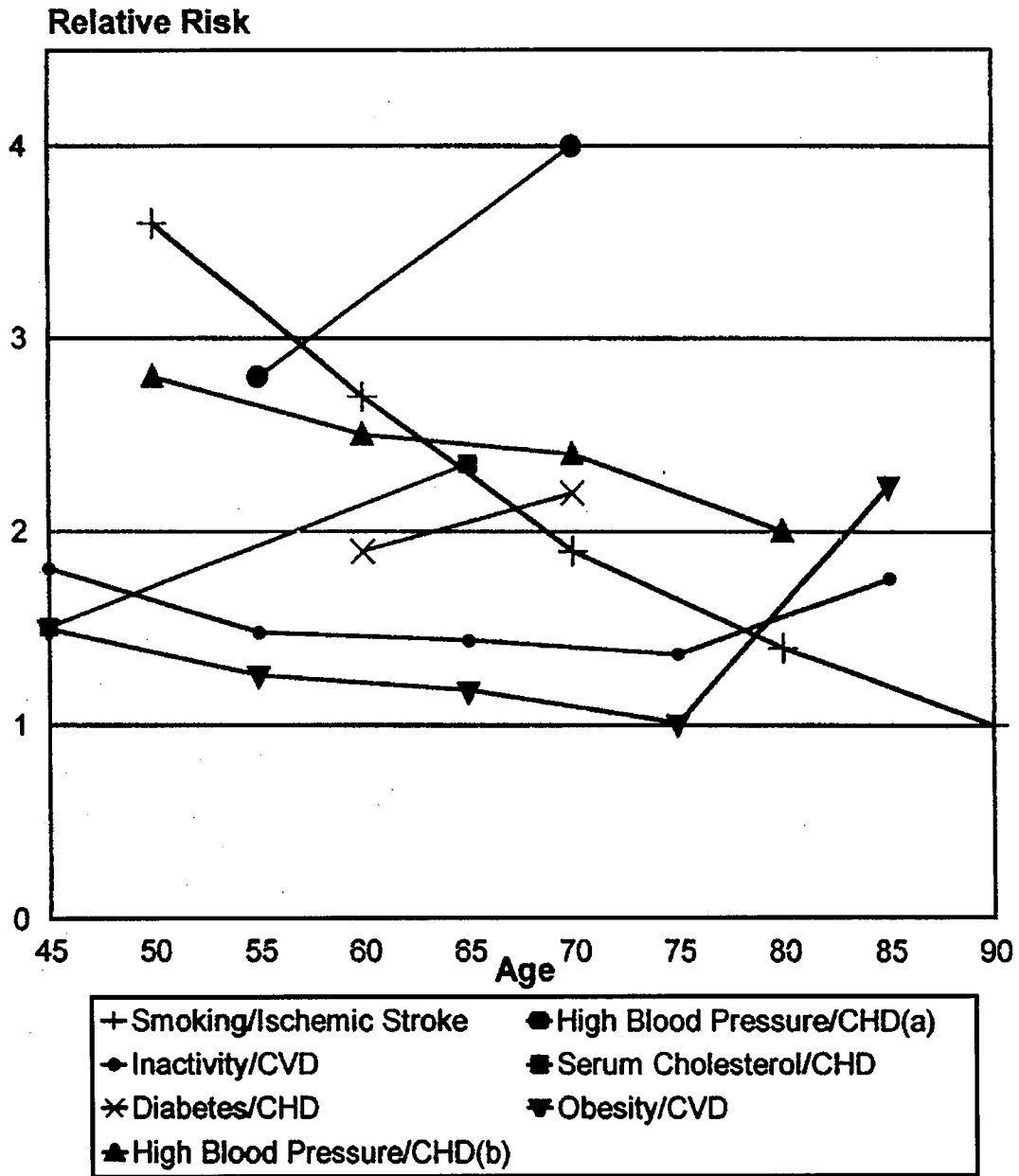


Figure 1 Examples of age-related patterns in risk factor-disease associations. Data are current (versus noncurrent) smoking and incidence of ischemic stroke in Rochester, MN (61); high blood pressure (>160/95 vs <140/90) and annual incidence of coronary heart disease in Framingham Heart Study (49) (a); high versus low systolic blood pressure (150 vs <122 mm Hg) and 12-year incidence of coronary heart disease in the Honolulu Heart Program (3) (b); high versus low levels of total serum cholesterol (6.7 mmol/liter vs lower levels) and mortality from coronary heart disease in the Charleston Heart Study (30); prevalent diabetes and risk of coronary heart disease in women in the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study (33); obesity (85th sex-specific percentile from NHANES II for body mass index versus lower levels) and leisure-time physical inactivity (reporting never swimming, walking, playing a sport, or exercising versus other); and 15-year risk of death from all causes in the Alameda County Study (GA Kaplan, unpublished analyses).

percentile from NHANES-II for body mass index) and leisure-time physical inactivity (reporting never swimming, walking, playing a sport, or exercising) show very slight decreases in the strength of association with 15-year risk of death from all causes over ages 40–49 to 70–79, with an increase for those 80 years or older (GA Kaplan, unpublished analyses). Analyses of the age-specific extent of intima media thickening of the common carotid arteries in the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study show even more variation, with no consistent pattern of either increasing or decreasing association with risk factors across the age spectrum for those 45–75+ years of age (23).

Thus, the assertion that risk factors generally become less important with increasing age, at least with respect to the above examples, is unsupported. In fact many different patterns are found. Faced with the multitude of patterns encountered in these examples, how is one to understand the origins of the myriad patterns that are found?

In many ways, the problem of understanding the age-specific pattern of risk factor associations with disease endpoints shares many features with other epidemiologic analyses. A full understanding requires consideration of subject selection, risk factor exposure, host characteristics, disease ascertainment, and study design. Figure 2, which provides the organization for the remaining discussion, presents a schematic representation of how the first four of these

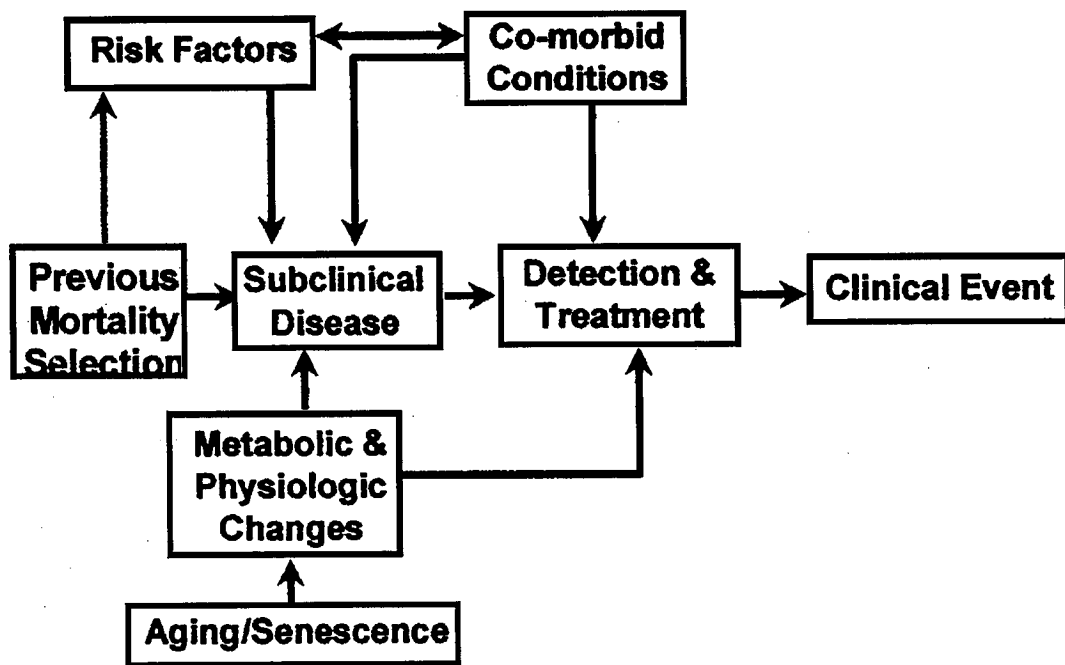


Figure 2 Factors determining trends with age in risk factor–disease associations.

factors interrelate and contribute to age-specific patterns and trends between risk factors and disease outcomes. Previous selection processes determine characteristics of the population that is exposed to risk factors, defined both historically and contemporaneously. The impact of these risk factors on disease initiation and progression is influenced by biologic characteristics of the individual, leading to early subclinical disease. These biological characteristics, some of which are patterned by age, may influence the detection and diagnosis of disease. Comorbid conditions may influence, or be influenced by, exposure to risk factors, progression to diagnosis, detection, or clinical event, and the ease of detection and diagnosis. Finally, the ability to view various aspects of this complex picture within an epidemiologic study will be dependent on features of the study design and analysis.

HOST CHARACTERISTICS

Physiological and Metabolic Differences in Older Persons

In general, physiological and metabolic function is altered in older persons. Age-related declines in the functional levels of most organ systems are well-documented (58). These alterations are usually gradual. There does not appear to be a particular age when they become prominent. Different organ systems may age at different rates, and there may be differences among populations in the trajectory of these changes. It is uncertain from both conceptual and methodological perspectives whether these changes are obligate and biologically programmed (i.e. natural) or whether they are caused by diseases and exposures that are at least potentially modifiable. Probably both are correct, but there are few studies that attempt to explore putative environmental exposures as causes of age-related physiological change. Evidence from rodent experiments that longevity and function enhancing can occur from prolonged caloric restriction (45) suggests that many age-related changes that appear obligate may be malleable if appropriate interventions can be identified.

There may be important analytical consequences of age-related physiological changes. Because of the diverse nature of these changes, factors that may be related to a given outcome or exposure of interest may also be changing with age (i.e. confounders and risk modifiers), and, if they are not fully accounted for, this could lead to altered risk estimates. For example, age-related changes occur commonly in pulse pressure, creatinine clearance, glucose tolerance (in Western populations), body fat composition, and pulmonary vital capacity. All of these may alter the effect of particular risk factors on cardiovascular outcomes as well as survivorship after disease onset, and they may not all be accounted for in various population studies. A prime example is that of coagulation factors. Several of these have been associated with increased risk of

myocardial infarction, and most of these factors increase with age (36). Determining these levels is complex and expensive, and these determinations are not performed in many cardiovascular risk studies, even if they might explain age-related changes in risk ratios. A further general problem is that, because age-related physiological changes are gradual, they are often difficult to summarize and may change over the duration of observation.

Even if the age-related factors mentioned above could be measured and accounted for in a particular study, many other host changes are occurring that could have important effects on exposure-outcome associations. For example, alterations in consumption and absorption of many nutrients occur with age in mammals (8, 44), and thus merely assessing dietary intake may not reflect the actual amount impacting on the host. This may be true for many common micro- and macronutrients in addition to the well-known example of vitamin B12 and its consequences. Further and sometimes subtle dietary changes may be occurring because of the increasing incidence of lactose intolerance with age (11), limiting intake of dairy products and consequent intake of calcium and vitamins A and D, which are important for several conditions. In addition, the decreasing ability to chew certain foods because of changes in dentition and gradual changes in food preferences because of alterations in taste and smell functions (52) may contribute to subclinical but biologically important dietary changes.

The absorption, distribution, and disposition of medications are clearly altered with age (56). Drug absorption, at least for certain agents, may be altered by changing intestinal physiology or dietary constituents. The kinetics of drug distribution in the body may be altered with age and metabolism, and excretion may be altered because of changes in liver function. Some of this may be adjusted for in the clinical-care process, but earlier and subtler changes may not be detected. The effect on outcomes of interest may be favorable or unfavorable. If a drug requires metabolism to an active form, then age-related changes may retard adverse events, as well as efficacy. If age-related changes deter metabolism or excretion of the active form, then concentrations and biological effects, desired or not, may be more common. All of this is critical in assessing drug-outcome associations.

The issues noted above for medications may also pertain to environmental chemical exposures. Absorption, metabolism, and disposition of these agents may be altered in the same way as are medications, with consequences and directional effects that may be difficult to predict. Age-related changes in handling of environmental xenobiotics have been reviewed (62), but much more work is needed to determine how these changes affect causal epidemiological studies. In addition to age-related changes in bodily handling of medications and environmental chemicals, the net biological impact of various chemical

exposures on the cell, organ, and organism is likely to be altered with age. For example, the older artery may be more susceptible to atherogenic influences (22). Another important example is the evidence, albeit incomplete, for an age-related decline in endogenous DNA repair, whether owing to intrinsic cellular events or exogenous environmental challenge (4). Thus, a given net exposure to a genotoxic substance, *ceteris paribus*, may have a greater impact in an older person, possibly leading to greater disease occurrence. Caloric restriction in animal models has been shown to retard age-related increases in oxidative cell damage and declines in DNA repair and apoptosis (61).

At the level of the individual, age-related physiological and metabolic changes may be biologically summarized in the phenomenon of homeostasis (1), a prominent concept in the gerontological literature. This can be defined as the ability to return to the previous physiological state after a challenge or stressor of some type. Homeostatic capacity is lower in infants when compared with that in young adults, but decline is also prominent in older persons. Examples include the higher case-fatality rate among elders that occurs for a given amount of physical trauma, such as in auto crashes (50), or the excess mortality that tragically occurs during extreme meteorological stresses (54). A clinical situation related to this is decreasing rates of wound healing among disabled elders (2). This human phenomenon may of course be related to the presence of clinical diseases, but it is real and probably not separable from "pure" aging, if that exists. In a certain sense, many diseases themselves and their treatments (such as general anesthesia and surgical procedures) may be considered as stressors and tests of the older host's homeostatic capacity, and that may in part explain shorter survival for a given level of disease among older persons. Based on the notion of homeostasis, it is possible that age-related changes in exposure-disease associations may be occurring because the number of incidental stressors and threats that occur in older persons may present a competing risk situation that alters the estimates of any one factor of interest.

Impact of More Advanced Disease and Comorbidity

Many diseases found in the elderly are chronic and progressive in nature and often evolve over long periods of time. Because of this, diseases will generally be more advanced than those found in younger persons. The higher prevalence of subclinical disease in the elderly may result in different risk factor-disease association in observational studies and treatment differences in clinical trials in older versus younger persons. In the Cardiovascular Health Study (MN Haan, unpublished analyses), for example, the internal common carotid arteries of 17% of those aged 65-69 were in the top quartile of wall thickness (≥ 1.95 mm) compared with 36% of those aged 80+. The impact of a risk factor or treatment on disease events in a sample that already has high levels of subclinical

disease may be attenuated, or the outcome may be different. In those with very high levels of atherosclerosis, it cannot be said that the disease is prevented by treatment, because it already exists, albeit in a subclinical form. Clinical manifestation of underlying disease may be precipitated by risk factor exposures that are more acute in nature (e.g. sudden stress, hypercoagulability, or vasospasm) than the more typical cumulative, progressive exposures. Thus, interpretation of age-specific differences in risk factor-disease associations must be within a framework that acknowledges the natural history of the particular disease in question and distinguishes between risk factors associated with disease progression versus initiation of acute clinical events.

Because most adult conditions increase in incidence and prevalence with age, comorbidity is common among older persons, and the presence of incidental illness may be a major cause for altered exposure-disease associations. These may co-occur because of exposure to a common risk factor, or one may be a consequence of the other and may affect another's disease progression. Comorbidity may influence case ascertainment/detection. Some illnesses may shape clinical priorities or treatment patterns and alter interest in new conditions, or they may lessen the likelihood of routine disease screening. For example, patients with Alzheimer's disease are less likely to receive routine screening tests such as mammograms (15). Comorbidity may alter disease presentation and outcomes because of combined bodily stresses. For example, both hypo- and hyperthyroidism may exacerbate heart disease primarily caused by other risk factors. Also, poorly defined conditions may alter the interpretation of exposure-disease associations. Frequently undiagnosed inflammatory arthritis in older persons may lead to decreased physical activity. If the latter is being examined as a cause of other conditions, the association may be altered because of confounding by comorbidity, a situation more likely to occur in older persons. A related issue is the occurrence of secondary complications of illnesses among older persons. Higher levels of secondary infections after influenza or increased rates of falls in disabled elders are examples of how diseases may be changed in presentation or outcome.

Multiple conditions often lead to polypharmacy (46), and each medication may have its own effect on an exposure or condition of interest. For example, using thiazide diuretics for hypertension may decrease risk of hip fractures (32), and using beta-blockers for angina or hypertension may reduce the risk of auto crashes (55). Although this situation is complex and dependent on the particular scientific question, it seems likely that the presence of other conditions, detected or not, can affect study associations. The number of potent clinical interventions, often not fully evaluated, could more likely modify the effects of a given exposure on a disease. This situation should always be explored in as much detail as possible.

AGE-RELATED ISSUES IN THE DIAGNOSIS AND DETECTION OF OUTCOMES

Disease manifestations in the elderly may differ from those in younger populations. Symptoms are often vague, subtle, and atypical and involve multiple systems. Functional declines may not be attributable to a specific cause but reflect systemic frailty and greater iatrogenic effects (57). Thus, some diseases may have altered clinical presentations in older compared with middle-aged adults. For example, there is the suggestion that myocardial infarction may be more often clinically silent among older persons, at least older men, possibly altering surveillance and detection rates (27). Certain important intra-abdominal inflammations such as cholecystitis or appendicitis may go undetected for longer periods of time (25), causing altered outcomes and increased mortality. Persons with diabetic neuropathy may have decreased pain sensation and thus may not easily sense certain incipient pathological changes. Overall, it is likely that the altered threshold for personal detection or recognition of signs and symptoms may change the presentation and natural history of various important clinical conditions.

Disease detection among elders may also be altered because of changing normative ranges of clinical laboratory measures, such as common biochemical or hematological determinations. The distributions of many of these values change with age, and leaving aside the issue of what is "normal," clinical decisions made from a laboratory that uses age-specific norms may be different from a situation in which the laboratory's normal range is the same for all adults.

DETERMINATION OF RISK FACTOR EXPOSURE

Respondent Characteristics

Changing cognitive function among older persons is well described, and that may alter epidemiological findings in several respects. For example, there may be altered recall of historical risk factors or prior medical conditions with increasing age, in addition to the longer period of time that is to be recalled. Measured cognitive function has been related to reliability of responses in questionnaire studies of older persons (9). For various reasons, there may be more difficulty with understanding various kinds of questionnaires, computer-aided assessment devices, or other data collection modalities. Altered vision and hearing may also play a role. Research aimed at improving the efficiency and accuracy of interviews among older persons by using cognitive mechanisms is increasing (24).

Cognitive impairment or dementia may be present in 5–20% of people aged 70+ and in 30–50% of people over age 85. This means that data collection may

require the help of a proxy respondent. The kinds of data that can accurately be collected may be limited to relatively factual information after the level and frequency of contact the proxy has with the respondent can be evaluated. Clearly, in these cases information on past exposures generally cannot be accurately obtained from interviews with either the participant or a proxy (38).

Data collection in older populations may differ from that in younger populations in the degree of accuracy and validity that can be obtained. Complex data collection may take more time than participant burden will allow or might have to be done in several stages, leading to increased costs. Even in the absence of frank cognitive impairment, retrospective recall of exposure may be less accurate as well, given the longer time period involved and greater distances in time from potentially key exposures such as occupational hazards.

Personal habits or behaviors often change at older ages, and these may have effects on exposure-disease associations. Some issues related to diet are noted above. As has been widely demonstrated, exercise and other habitual physical activity may have a potent impact on many biological processes and disease occurrence, and as age-specific physical activity declines for various reasons, the interaction with a risk factor of interest should be considered. Also, in general, older persons have less exposure to substances that are potentially harmful. Cigarette smoking and alcohol use decline with age, as does illicit-substance use. All of these may alter main exposure-disease relationships, and they are not always queried in detail.

There may be important changes in environmental exposures that lead to altered exposure-disease association among older persons. A major reason is fewer workplace exposures. One of the most important areas often not assessed, except when it is the specific scientific object of interest, is the workplace environment. Currently, the majority of Americans are retired by age 65 years (14), and, thus, potentially hazardous or biologically active environmental exposures are likely to be curtailed. Although the net biologic impact on disease pathogenesis can only be speculated, there are effect modifiers that are not otherwise accounted for. Retirement may lead to altered ancillary activities, such as exposure to automobile commuting, road fumes, accidental injuries, and common infections related to high levels of social and public exposures, such as from crowded public transport vehicles. On the other hand, whereas workplace exposures are usually curtailed, exposures related to recreational endeavors may conversely be increased. Thus, increased recreational travel or hobbies may be associated with alternative environmental exposures.

An active social environment has been postulated to confer health-giving properties in several ways. To the extent that the social environment becomes limited with age, for reasons of disease, disability, or changes in social roles, there may be both negative and positive effects on health status and biologic

systems. An example of a positive health influence is the potential of less exposure to influenza virus among those who are homebound.

Exposure Measurement

TIME OF MEASUREMENT Most studies of the elderly focus on gradually progressive, chronic diseases such as cardiovascular disease, dementia, arthritis, and cancers. Often, these diseases develop over 10 to 40 years. The general assumption about the influence of risk factors in this process is that chronic exposures slowly lead to cumulative damage and disease that may manifest itself clinically by reaching a certain level of damage, initiating other pathophysiological changes, or increasing vulnerability to acute precipitants. A preliminary but critical issue is the timing and duration of exposure to a particular risk factor. If exposure to a risk factor of interest extends through most of adult life, possibly beginning in childhood or even prenatally (e.g. hyperlipidemia or a long history of cigarette smoking), the biological effects are likely to be cumulative and possibly advanced at older ages. Assessing the presence of such a risk exposure later in life and following the population for disease onset really represents the net effect of a more advanced and possibly different biological process than in a situation in which the exposure occurred only in late life. Thus, in addition to exposure duration, the timing and point in the life cycle when exposure occurred must be considered when assessing age-related differences in risks and rates of disease associated with a risk factor. Analyses should be grounded in conceptual models that help to separate the effects of chronic versus acute exposures.

Some age-related differences in risk levels may be caused by cohort effects, which are difficult to overcome in experimental designs. Also, few studies measure risk factors over a 30- to 40-year time period. Thus, there is little information on the tracking of risk factors into older ages, and information about past exposures is likely to be inaccurate and probably subject to recall bias. When such measures are available, they seem to be powerful predictors of a wide range of health outcomes. For example, in the Alameda County Study (37), 29-year cumulative measures of economic disadvantage were strongly associated with later disability, depression, cognitive problems, hostility, and lack of optimism. The level of detail about exposures in the distant past is also likely to be fairly crude (e.g. "yes/no" responses), which will add further to measurement error. Furthermore, it is only recently that sophisticated methods for analysis of such longitudinal data have emerged (12).

Varying lengths of time between risk factor measurement and ascertainment of outcomes can also introduce complexity. For example, an association between total serum cholesterol and incidence of coronary heart disease was not seen in the Framingham Study when cumulative 2-year incidences of coronary

heart disease were used (6), but it was found when 16-year incidences were used (5). Although not well studied, it is plausible that events occurring soon after risk factor measurement in older persons more heavily represent pathways involved in the precipitation of acute events, as opposed to long-term chronic processes (29). Thus a certain amount of pathophysiologic heterogeneity is introduced in studies with widely varying follow-up times or when comparing studies with different lengths of follow-up. Since both longer follow-up periods and more severe subclinical disease will be associated with older age, an additional complexity is introduced in interpreting age-related trends in risk factor association.

For many of the above reasons, the association between exposure and disease may differ for past compared with current exposures. However, few studies have systematically compared cumulative versus contemporaneous measures of risk factors or examined the relationship between the two. Harris et al (19) were able to use the considerable longitudinal data available in the Framingham Heart Study to examine the association of risk of cardiovascular disease with current and prior measures of blood pressure, as well as the slope of changes in blood pressure in those who survived to age 65. Knowledge of systolic blood pressure history and changes added to the ability to predict cardiovascular disease development after age 65.

Analyses of the association between weight and coronary heart disease in Cardiovascular Health Study participants (aged $\geq 65+$) (21) indicated that weight at age 50 was positively associated with coronary heart disease risk whereas weight at the beginning of the study, when participants were ≥ 65 years, was not. Similarly, in the Whitehall Study of British civil servants (51), there was an indication that the association between serum cholesterol levels and coronary heart disease mortality was stronger when the measures were obtained earlier. Changes in weight between middle/late-middle age and old age have also been shown to be associated with mortality from all causes (35), risk of coronary heart disease (20), and risk of hip fracture, physical disability, low mental status score, and low physical activity (33).

QUALITY OF MEASUREMENT As indicated above, age-related changes in risk factors may reflect changes in health status, behavior, social roles, environmental exposures, cohort effects, or, to be discussed below, selection effects. There also may be increases in the imprecision of measurement owing to cognitive limitations, respondent burden, or the use of proxies. All of these will tend to influence the magnitude and precision of risk factor associations with disease and functional outcomes, with the extent of these effects increasing with age. Furthermore, the impact of comorbid conditions on risk factors can

be substantial, as many chronic and acute conditions will tend to exert large influences on the prevalence and trajectories of risk factors. Often, the impact of comorbidities is accounted for by statistical adjustment. However, given the cross-sectional relationship between the risk factor of interest and the comorbid conditions, such analyses can lead to misleading results (29).

In general, duration of exposure to a risk factor will be correlated with age. This correlation between cumulative measures of exposure and age can create analytic and conceptual problems. For example, if one is interested in the relationship between length of time since quitting smoking and risk of disease, the length of time since exposure will be correlated with age of the ex-smokers. The end result is that it is difficult to be confident about statistical solutions to the separation of age and cumulative exposure effects.

OTHER METHODOLOGIC CONCERNS

Sampling and Representation

The practice in many epidemiologic studies is to restrict the initial sample to people who can participate fully. Institutionalized people are frequently excluded. For diseases that lead to institutionalization and are thus common in nursing homes and other long-term care populations, prevalence can be substantially underestimated in noninstitutionalized populations. Given the high prevalence of various cognitive and functional limitations in the very old population, samples restricted to nonimpaired individuals would not be representative of the older population, limiting generalizability. A significant proportion of people with dementia, incontinence, and other diseases of aging/frailty are institutionalized. Magaziner (39) has estimated that about 30% of all dementia patients are in institutions. Incontinence is also common in older populations and is a major predictor of institutionalization (10, 48). The socially isolated elderly are also more likely to be institutionalized. The effect of such exclusions on risk estimates might be to attenuate them because individuals who had been more vulnerable to disease caused by exposure would be less likely to be included. This would leave in the sample mainly individuals who were not exposed, were slower to respond to exposure, or who were not vulnerable. In clinical trials, in which randomization may ideally balance out confounding factors, the issues of representation, adherence, and retention still remain. Dropout rates among older persons may be greater than those among younger persons and may vary in active treatment arms, depending on respondent burden, side effects, caregiver burdens, illnesses, and limitations. If dropout or nonadherence is greater in those who are older (frail or ill), the inclusion of elderly in clinical trials may reduce the difference between treatment arms. Since event rates are higher in

older people and power is potentially increased, this is often used as a reason to include elderly. However, this is not without its costs in terms of poorer retention and adherence, which can attenuate treatment effects.

Gross functional limitations such as difficulty in walking are present in as many as 20% of people aged 75+ (43). Most research protocols involving any clinical assessments require participants to complete at least one clinic visit, and this de facto restricts the sample to more functional elderly. Thus, certain kinds of exposures or conditions may be lower in recruited samples or distributed differently by subgroup in the sample population than the actual population.

Comorbidity

A relatively unique characteristic of older populations is the coexistence of several chronic conditions. As indicated above, treatment of one condition may influence the outcome of others, and treatments for multiple conditions may interact in poorly understood ways. Thus, the complexity of disease in older populations complicates analysis and understanding of risk factor–disease associations. The tendency has been to construct scales that add up all comorbid conditions (7). This approach may allow a general assessment of chronic disease burden and be predictive of broad patterns of mortality outcomes, but the process of combining conditions into a single scale obscures considerable pathophysiologic detail that may have etiologic importance. For example, it does not allow an examination of the interactions between specific conditions and does not consider shared or overlapping risk factor or biologic pathways. The net result is that the common approach of taking comorbid conditions into account through multivariate adjustment may be relatively uninformative.

Competing Risks

Competing risk refers to the problem of estimating the risk of a disease while other risks are operating in the same population (53). In the simplest terms, competing-risk analysis seeks to estimate risks of death from a specific cause when a second (or third) potentially life-threatening cause is eliminated and to estimate net probabilities of death when competing causes are eliminated. If the risk of a competing cause is quite low relative to the risk of the cause under study, the competing cause will have little effect. However, in older populations with high levels of comorbidity, this is not likely to be the case. An additional problem is the underlying assumption that the competing causes are independent and that the mechanisms underlying them act independently. Clearly, this is not the case with many co-occurring diseases, as discussed above. When they are not independent, as in the example of smoking, coronary heart disease, and lung disease, the cause-elimination approach may not accurately reflect risk. For example, in the Cardiovascular Health Study, 18% of those

with lung disease also have had a myocardial infarction, and 11% of those with myocardial infarction have lung disease (MN Haan, unpublished observations). Thus, elimination of myocardial infarction as a cause will remove about a fifth of lung disease cases. It is not clear how one can eliminate a cause that co-occurs with another cause. The joint occurrence of disease may result from common exposure, such as smoking as etiologic for both coronary heart disease and lung cancer. Even if there is no common etiologic risk factor exposure, one condition may become a risk factor for another, a so-called "interfering cause" (29). Although these issues are not restricted to older populations, they have more impact than in younger populations because of the greater co-occurrence of diseases. To the extent that competing causes are operative, they will have an impact on the observation of age-related trends in the association between risk factors and mortality.

Selective Survival

As noted above, higher-risk individuals may be selected out of the population at earlier ages. Although this applies to any age cohort, the forces of prior selection are much stronger in older populations. The analysis of the consequences of selective survival is complex and can lead to a variety of age-related patterns in differential survival (29, 59). It is useful to think of three ways in which selective survival might influence age-related trends in risk factor–outcome associations. If those with a particular risk factor experience higher and earlier mortality, then the distribution of risk factors in the survivor population would be altered relative to the "original" distribution and should reflect lower levels of exposure, because those with high levels of risk factors are more likely to have been removed from the population. Second, it is possible that there are unmeasured differences in susceptibility to the risk factor among both those previously exposed and those unexposed. Third, the survivors may have other characteristics, genetic or environmental, that prevent or slow the progression of disease, shifting the onset to a later age.

In the first scenario, the distribution of risk factors has been changed, but assessing the strength of the association between the risk factor and some outcome is not strictly dependent on the prevalence or distribution of the risk factor. In this case, an age-related decline in the risk factor–outcome association would not necessarily follow. In the second case, one would expect a decline in the strength of the association between the risk factor and outcome as the exposed group becomes progressively more composed of those who are not susceptible to the risk factor. However, Vaupel & Yashin (59) have shown how a variety of survival patterns can be generated by unmeasured heterogeneity in susceptibility depending on various assumptions. Note that in the presence of unmeasured susceptibility this becomes somewhat circular. Susceptibility

comes to be defined by seeing who survives and who does not, and, by definition, those who survive are less susceptible. Although there undoubtedly are differences in susceptibility to various risk factors, the circularity of most uses of this term does not naturally lead to improved understanding of differential survival patterns.

The third pattern, in which disease may be postponed to later ages rather than being completely prevented, has been less discussed and is illustrated by the black-white mortality crossover (42). Age-adjusted mortality rates are higher for blacks than for whites. However, beyond 70 years of age, mortality rates for whites exceed blacks as white mortality rates accelerate more rapidly than blacks. One can view this as a consequence of earlier mortality in higher-risk blacks, but it can also be viewed as resulting from postponement of disease in whites, since white rates do accelerate but at a later age. If selective survival of lower-risk people were an important factor in this relationship, one would expect to see a lower prevalence in risk factors among blacks at older ages, but there is no evidence for this (40). The evidence suggests that older blacks have higher levels of many important risk factors.

Ceiling Effects

Age-related declines in the strength of association between a risk factor and outcome may also reflect ceiling effects (29). For example, in the Alameda County Study (30), the 17-year mortality rate among those 70–94 years of age was 80%. In such cases of high mortality, the death rate among those not exposed to the risk will begin to approach the death rate of those exposed, and relative risk and ratio measures will diminish. Similar problems present themselves with outcomes in survivor populations. As discussed above, the prevalence of many disease conditions in older populations is very high. In those over 80, cognitive impairment/dementia may occur in as much as 50% of the population (13). Benign prostatic hypertrophy occurs in 80% of men over 80 years of age, and osteoarthritis is diagnosed in 70% of men and women over age 80 (16, 17). When the background level of disease is so high, ceiling effects will make it very difficult to detect strong associations with risk factors. In other words, when nearly all the population has the disease, there is very little room for any additional excess risk associated with a risk factor. An important corollary is that, in cases in which outcome rates are high, absolute levels of risk should be examined as well as relative risks, and the use of models with proportional hazard assumptions should be carefully evaluated (26).

Measures of Association

The measures of association used in assessing risk factor–disease relationships may also yield different age-related patterns in strength of association. As a

number of authors have pointed out, conclusions about the impact of risk factors with increasing age are dependent on the measure of association that is chosen (3, 29, 41, 49, 55). Each of these papers presents data illustrating cases in which the association between a risk factor and an outcome declines with the use of relative risk measures, but increases with the use of excess risk measures. Stamler (55a) used data on the association between elevated serum cholesterol (182 mg/dl versus lower levels) and 6-year risk of coronary death in the 356,222 screened subjects, aged 35–57, in the Multiple Risk Factor Intervention Trial, to compare relative and excess risk. Over the age range of 35–57, the relative risk almost halved (from 3.3 to 1.8 years), whereas the excess risk more than quadrupled (124.8/100,000–705.0/100,000). Although the relative risk is often taken as the measure that is more relevant to etiologic inference, excess risk measures better represent the population burden of the risk factor. Clearly, the choice of which measure to use will reflect the specific goals of the investigator. However, it is clear that conclusions concerning the relative importance with increasing age of a risk factor will depend on the choice of measure.

CONCLUSIONS

No simple conclusions can be drawn concerning the relative importance of risk factors in younger versus older populations. As in examining any body of epidemiologic knowledge, it is important to interpret results from a perspective that includes pathophysiologic and biologic considerations, issues of selection, exposure and outcome assessment, and choice of analytic techniques. Public health is ill served by simplistic statements about the impact of a particular risk factor increasing or decreasing with age, without a full consideration of all of these factors. On the other hand, the aging of the population and the growing evidence that many risk factors do appear to be important determinants of the health and well-being of older populations argue for an increased focus on disease prevention and postponement and on enhancement of function in the elderly.

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