

Left-truncated Data With Age as Time Scale: An Alternative for Survival Analysis in the Elderly Population

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Background. The standard approach for survival analysis of the elderly population is to define the survival time as the elapsed time from entry into the study until death, and to adjust by age using stratification and regression procedures. However, the interest is in the study of the aging process and the risk factors related to it, not in the use of time-on-study as the time scale. Here, we present methods to use age as the time scale and compare inferences and interpretations with those obtained using the standard approach.

Methods. A total of 1,315 individuals aged 65 years or older from the city of Barcelona, Spain, were interviewed in 1986 (baseline). The vital status of the cohort was assessed in October 1994. To illustrate the usefulness of age as time scale (alternative approach) instead of time-on-study in the survival analysis of the elderly population, both methods were used to assess the relationship between baseline functional capacity and mortality.

Results. Using the alternative approach, we observed that 50% of the sample died at age 80.6 years; this information could not be estimated with the standard approach. Using age as a covariate in the standard analysis with time-on-study as the time scale and using age as the time scale in the alternative analysis, the association of functional capacity at baseline and mortality was of similar magnitude under both analyses. Nevertheless, using the alternative approach, relative risks were slightly lower, and the adjustment by age was tight and was not subject to the inherent assumptions in regression models of the functional relationship of independent variables with outcome. We illustrated the methods with fixed covariates (i.e., gender) and baseline values of time-dependent covariates (i.e., functional capacity), but we discussed the extension of our methods for the analysis of time-dependent covariates measured at several visits in a cohort study. Methods proposed here are easily implemented with widely available statistical software packages.

Conclusions. Although the use of standard survival analysis generally produces correct estimates, the use of age as time scale is deemed more appropriate for survival analysis of the elderly: Inferences are easier to interpret and final models are simpler. We therefore recommend the use of age as time scale for survival analysis of the elderly population.

THE stratum of population older than 65 years is growing considerably faster than the rest of the population. The projections for the period 2000–2025 are that the elderly population will increase an average rate of 2.6%, compared to 1.2% for the overall population (1). As a consequence, aging of the elderly population itself is expected (2). The aging process may be associated with a higher risk for chronic diseases and mortality (3). Therefore, older adults have become a very important focus of interest for clinical and epidemiological research.

Cohort studies have been useful for the identification and understanding of how different risk factors may lead to premature mortality or loss of functional capacity at older ages (3). Typically, the putative risk factors are assessed at baseline, and individuals are followed with “dead” as the endpoint. The standard, “time-on-study” approach for the analysis of this type of data is to define survival time as the elapsed time from entry into the study until death. However, the entry time into the study as origin point lacks the characteristics of a meaningful interpretation that other

points may have (e.g., the moment when an intervention is carried out, a point of change in the disease or when a disease begins, or even when a person is classified as an “elder”). In studies of the elderly population the interest is in the study of the aging process, and this process has been conventionally considered to begin when the individual is age 65 and not when the subject enters the study cohort. Study subjects therefore are included in the sample if they are alive at the date that the study started and if they have reached age 65 at the entry time, that is, if their survival time exceeded that age. As a matter of fact, we are not truly interested in the mortality rate as a function of time since recruitment, because this is a function of the study duration, instead of the mortality rate as a function of the aging process duration. In addition, age per se is associated with survival and with the risk factors of interest; there is a high correlation of many of the risk factors with increasing age, such as blood pressure and cholesterol (4), among others, and therefore age acts as a confounder factor. The standard statistical procedures partially overcome

this fact by means of adjusting by age (5), stratifying by age (6), or by computing age-adjusted incidence rates (7); however, it is necessary to take into account at what ages the risk factors are measured (8), because, for example, to be disabled at age 90 is not the same as to be disabled at age 67.

An alternative approach is to consider the survival time as the elapsed time from age 65 until the event of interest. In this approach, the time scale is age and not the time in the cohort. Thus, this approach directly takes into account the age effect on mortality, adjusting automatically for the confounding effect of age. This approach will allow us to draw individual inferences at specific ages (i.e., the survival probability will be based on an individual aged x years instead of an individual who has spent y years in the study cohort), and it would provide a more understandable interpretation (9). These and other related issues were discussed recently by Korn and colleagues (10).

The alternative approach is more appropriate for survival studies of elderly populations where the interest is in describing the factors that modify the hazard of death after a specific age, say, 65 years. In observational studies, individuals enter the study at different ages, but those who have entered the study after the origin point (older than 65 years) enter "late" into the observation (left-truncation) and their peers who died before the study started are not observed. Usually, the data are right-censored; that is, the event of interest (death) is not observed at the end of the study (either because the individual was lost to follow-up or was alive at the end of the study). In these situations, where the observed data are left-truncated and right-censored, one needs to use the extension of the standard proportional hazards model by incorporating the delayed entries.

The aim of this research is to illustrate the usefulness of taking age 65 as the origin point for the analysis of survival time in elders, instead of the date when the study was started.

The time scale of the analysis is age, which is the canonical scale in a study that attempts to identify factors that increase the risk of death after controlling for the aging process. The results of an 8-year study of elderly people living in the city of Barcelona, Spain, are used to implement this alternative approach for right-censored and left-truncated data. Here, we compare the inferences regarding the relationship of baseline functional capacity and mortality, when using as time scale the time since entry into the study (time-on-study) and the time elapsed since age 65 years (age as time scale). Although the methods have been used to describe incidence of AIDS in cohorts of young homosexual men infected with HIV (11), there is not, to our knowledge, a report explaining the methods using age as time scale in the elderly population, for which this is of prime importance.

METHODS

Subjects

The data are based on a longitudinal study of a sample of persons age 65 and older from Barcelona, Spain. The aim of the study was to assess the relationship between health status, health-related behaviors, the use of health services,

and functional capacity with subsequent mortality. Among these factors, we chose functional capacity to assess the relationship with mortality. Details of the design and sampling methods of this study have been previously published (12,13). Briefly, a total of 1,315 individuals, 809 females and 506 males, were interviewed at their homes between January 1986 and January 1987. A second home interview was carried out between July 1993 and July 1994. After approximately 8 years of follow-up (October 1994), the vital status of the whole cohort was assessed using the Local Census Register of Barcelona and the Regional Mortality Register of the Generalitat de Catalunya by a confidential record linkage. If the participant did not appear in registers because he or she had moved away from the area, an active search was carried out.

Among the 1,315 participants, 805 (61.2%) were documented to be alive at the end of the follow-up in October 1994; 452 (34.4%) had died, 37 (2.8%) were lost to the follow-up, and 21 (1.6%) could not be traced. We have restricted our analysis to those individuals for whom information on vital status at the end of the follow-up was available ($n = 1,294$), and those subjects who were lost to follow-up were considered as right-censored at the age they were considered lost from follow-up.

Furthermore, because the main interest was to describe the relationship between functional capacity and mortality in individuals between 65 and 90 years of age, we further restricted our analysis to those who were younger than 90 years at the time of entry into the study ($n = 1,275$).

Functional capacity was measured based on the difficulty or need of help in carrying out nine basic activities of daily living (ADLs). These activities were: walking, going up/down stairs, bathing, using the toilet, brushing hair/shaving, dressing, sitting, going outside, and eating. Individuals were defined as "disabled" if they reported being unable to perform one or more of the activities without assistance or having difficulty in performing them and "not disabled" when they reported being able to perform all the activities without any difficulty. The survival patterns after 8 years were compared in these two groups of elders defined by their functional capacity. In the standard analysis, when time in the study is taken as the time scale, age was categorized in three groups: younger than 74 years, between 75 and 84 years, and older than or equal to 85 years. The multivariate analysis using Cox regression was performed, stratifying by gender.

Statistical Methods

To assess the relationship between functional capacity and mortality, we analyzed these data using two different approaches. In the standard approach, time since entering the study was considered as the time scale; in the alternative approach, age minus 65 was taken as the time scale. Some minimal notation required for the analysis is described briefly below.

Let Y be a variable measuring the exposure time in years or longevity process, that is, the time from entry into the study (when the cohort is selected) until death or emigration if it occurred before October 1994. Let W be the delayed entry (14), that is, the elapsed time (in years) from

reaching age 65 until the individual was recruited. Let T be the complete longevity process, a random variable denoting the residual survival time since turning 65 until death or exit from the study: $T = W + Y$. We define δ as the censoring indicator, that is, $\delta = 1$ if we observe the event of interest (death) during the follow-up, and $\delta = 0$ otherwise. We assumed that the delayed entry process and the censoring mechanism are independent of the longevity distribution.

The Kaplan-Meier standard approach for right-censored data (15,16) is based on the observable data (Y, δ) and estimates the survival function by:

$$\hat{S}_1(y) = \prod_{j|y_j \leq y} \left\{ 1 - \frac{d(y_j)}{r(y_j)} \right\}, \quad (1)$$

where $d(y_j)$ is the number of deaths at time y_j , and $r(y_j)$ is the number of individuals at risk of dying at time y_j .

If age is taken as the alternative time scale, the estimator for the survival function when data are both right-censored and left-truncated (16,17), is based on the observable data (W, Y, δ) . This estimator is given by:

$$\hat{S}_2(t) = P(T \geq t) = \prod_{j|t_j \leq t} \left\{ 1 - \frac{d(t_j)}{r(t_j)} \right\}, \quad (2)$$

where, as before, $d(t_j)$ is the number of deaths at time t_j , but the number of individuals at risk at time t_j , $r(t_j)$, only includes those individuals who have entered the study at an age younger than $t_j + 65$. Note that, in contrast to the standard situation, where $r(y_j)$ decreases monotonically, the number of individuals at risk $r(t_j)$ may fluctuate dynamically with time t .

Figure 1 illustrates the above variables (W, Y, T , and δ) for four different individuals. Individuals A and B entered the study at 65 years of age, thus $w = 0$ for both of them. Individual A died during the study at age $65 + y$, thus $\delta = 1$, and individual B was alive at the end of the study when she was $65 + y$ years old, thus $\delta = 0$. On the other hand, individuals C and D entered the study at age $65 + w$, thus $w \neq 0$ for both of them. Individual C died during the study at age $65 + y + w$, thus $\delta = 1$, and individual D was alive at the end of the study, when he was $65 + y + w$ years old and $\delta = 0$.

An important feature of the proposed methods is that individuals are not considered at risk prior to the age at which they entered the study. Specifically, individual C does not contribute to the estimation and hypothesis testing at the time that individual A develops the event of interest.

Parallel to the extension of the Kaplan-Meier methods presented here, the methods of the proportional hazards model can also be extended for the estimation and hypothesis testing of relative hazards measuring the association between risk factors and survival with age as the time scale (15).

The methods presented here can be implemented with several statistical packages including S-plus, SAS, STATA, and EGRET. The Appendix includes the commands used to implement the proposed methods.

RESULTS

The distribution of the main variables of the study cohort at baseline is shown in Table 1. Among the male popula-

tion, 198 died and 297 were alive or were lost during the follow-up. The median age at entry was 75 years among those who died during the study and 71 years for the censored ones. Note that there is a large proportion of individuals who entered the study when older than 74 years. The median follow-up time for the censored individuals was 8.3 years. The median of the survival time was similar for both genders. Concerning the functional capacity, we observed that those individuals alive at the end of the study were significantly less disabled than those who died during the study ($p < .001$). Among women, an analogous pattern for age at entry and for the follow-up time was observed. The median age at entry was slightly higher for the uncensored group. Concerning the basic activities of daily living,

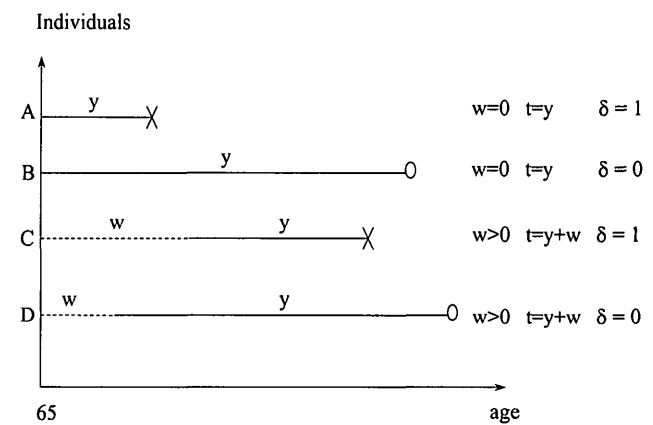


Figure 1. Definition of survival time. y = time from entering the study until death or emigration; w = time from reaching age 65 until the recruitment into the study.

Table 1. Age, Follow-up, Survival Time, and Functional Capacity of the Elderly Cohort

	Men		Women	
	Uncensored (n = 198)	Censored (n = 297)	Uncensored (n = 194)	Censored (n = 586)
Age at Entry				
Median	75	71	76	71
Range	65-87	65-90	65-89	65-90
65-74	49.0%	74.1%	37.6%	66.9%
75-84	47.5%	22.9%	52.6%	25.4%
> 85	3.5%	3%	9.8%	7.7%
Follow-up (y)				
Median	4.1	8.3	4.4	8.3
Range	0.1-8.5	0.4-8.9	0.1-8.7	0.4-8.9
Survival Time (T = W + Y)				
Median	14.1	14.0	16.2	14.5
Range	0.2-24.7	1.4-25.0	1.5-24.7	0.4-25.0
Basic ADLs				
No Disability	57.6%	76.8%	39.7%	62.5%

Notes: Uncensored = died during the study; Censored = alive or lost to follow-up; ADLs = activities of daily living.

women presented a lower level of no disability than men ($p < .001$).

In order to compare mortality of men and women using the standard survival approach, we split the sample into age categories (65–74 years, 75–84 years, and ≥ 85 years) and present the corresponding survival curves (Figure 2). A worse survival experience was observed for men in each age stratum. Because age is taken care of by definition (Figure 3), the alternative approach may be represented in one graph. We were able to assess the differences, when they existed, between men and women by performing a log-rank or Wilcoxon test. In contrast, using the standard approach we had to use some technique that allowed us to join the three different survival curves and then carried out an overall log-rank or Wilcoxon test.

To illustrate, Table 2 presents the estimation of the median and the first and third quartiles of the survival time for the male group using the two approaches. While in the standard case we could only estimate up to the first quartile, in the alternative approach the three quartiles were estimable from the data. Among men older than 65 years, 50% lived to over 80.56 years (i.e., $80.56 = 65 + 15.56$). Analogously, among those who were functionally free of disability, 75% survived 74.39 years, 50% survived 81.9 years, and 25% survived 87.45 years. In contrast, among functionally disabled individuals, 50% died before age 76.11. Figure 4 shows the survival curves by baseline basic ADL categories, when using the alternative method.

It is important to note that the Kaplan-Meier curves shown in Figures 3 and 4 correspond to fixed (i.e., gender) and time-varying (i.e., disability) risk factors, respectively. The interpretation for a fixed covariate is straightforward, but for a time-varying covariate the survival functions correspond to those while the disability status remains stable. Later in this article, we indicate how to extend the proposed methods to incorporate measures of time-varying covariates beyond those obtained at baseline as presented here (see Discussion).

To assess how functional capacity predicts survival, we carried out a multivariate Cox proportional hazards model for both survival approaches. Table 3 gives the estimates of the relative hazard of age and functional capacity. Note that age is taken into account in the definition of the time scale and thus was not entered in the alternative model. Both methods show that the risk of death of a functionally disabled man is approximately 1.8 times higher than the risk of a functionally nondisabled man, irrespective of which methodology was used. Similarly, functionally disabled women had approximately 2.0 times higher risk than functionally nondisabled women. However, we observed that the estimated risks were attenuated in the alternative approach for both (male and female) models.

DISCUSSION

The aim of this research was to show that the use of age instead of time-on-study as the time scale is an appropriate way to handle survival analyses of the elderly population. An advantage of the methods proposed is that they provide the juxtaposition of all the different periods provided by different individuals, and in doing so one obtains estimates

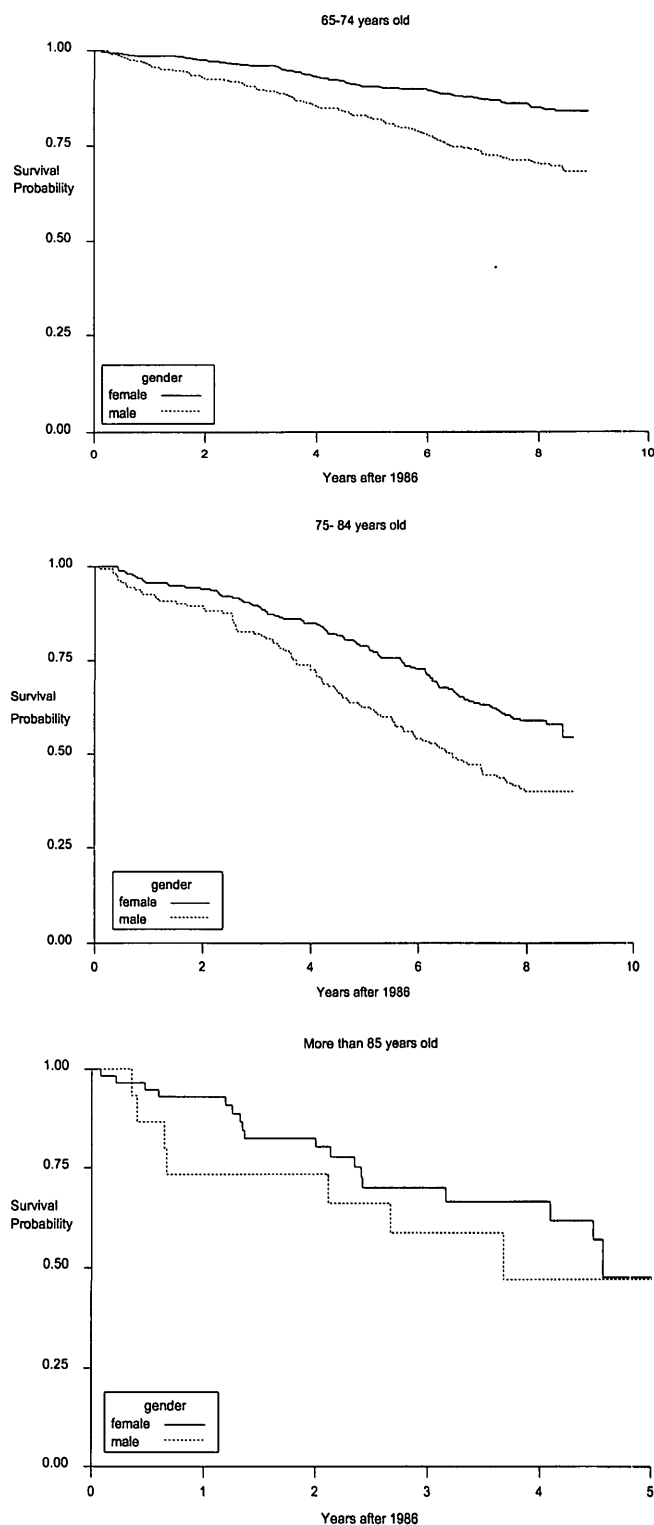


Figure 2. Survival curves by gender stratifying by age (standard approach: time-on-study as time scale).

of the survival probabilities at every age in groups that are homogeneous according to the risk factors considered in a given analysis. Another advantage of the proposed alternative approach is that it has a more straightforward interpretation of mortality, as it is free of the confounding effect of age, which is automatically taken into account as the mea-

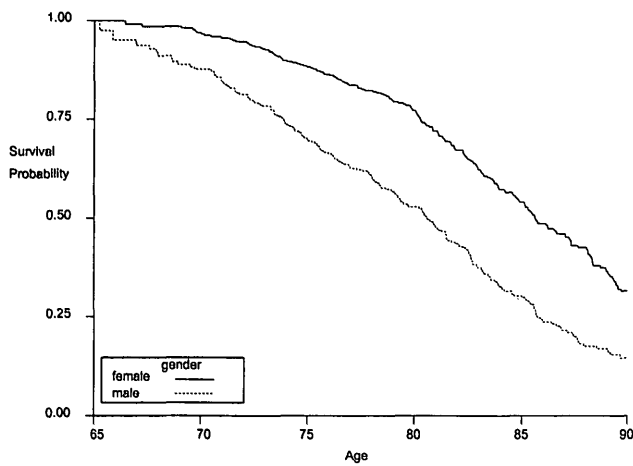


Figure 3. Survival curves by gender (alternative approach: age as time scale).

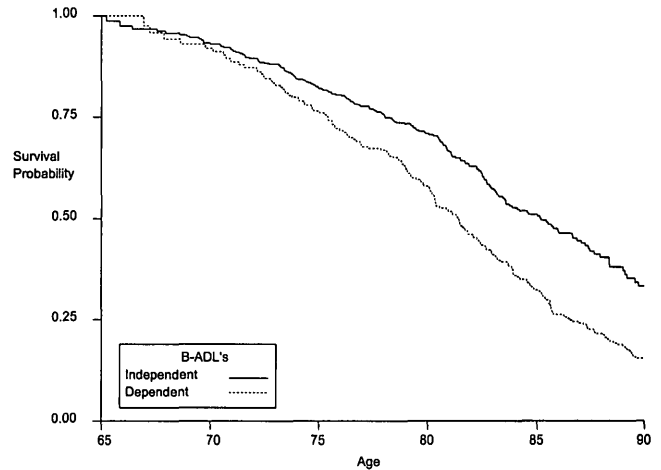


Figure 4. Survival curves by functional capacity using age as time scale. B-ADLs = basic activities of daily living.

Table 2. Median, First, and Third Quartile of Elderly Men by Baseline Functional Capacity and Type of Survival Analysis Approach

	Time Scale: Time-on-Study (standard)			Time Scale: Age (alternative)		
	Q1	Median	Q3	Q1	Median	Q3
Overall	4.92	—	—	8.82	15.56	20.67
Basic ADLs						
No disability	5.90	—	—	9.39	16.90	22.45
Disability	3.29	6.64	—	6.32	11.11	17.10

Notes: Q1 = First quartile; Q3 = Third quartile; ADLs = activities of daily living.

Table 3. Proportional Hazard Regression Stratified by Gender for Both Analytical Approaches: Standard (Time-on-Study as Time Scale) and Alternative (Age as Time Scale)

Covariate	Men		Women	
	Standard RH (95% CI)	Alternative RH (95% CI)	Standard RH (95% CI)	Alternative RH (95% CI)
Age				
65–74 years	1		1	
75–84 years	2.25 (1.68–3.00)		2.80 (2.06–3.82)	
>85 years	3.24 (1.39–7.59)		6.33 (3.64–11.01)	
Basic ADLs				
No disability	1	1	1	1
Disability	1.84 (1.38–2.46)	1.77 (1.32–2.36)	2.10 (1.56–2.83)	1.92 (1.43–2.59)

Notes: RH = relative hazard; ADLs = activities of daily living.

sure of survival time. In fact, the survival curves with this method are more similar to those describing general population mortality.

A drawback of the standard approach is that it did not allow us to estimate either the median or the third quartile for the survival time of the functionally nondisabled individuals. This happened because the standard approach does not maximize the available information of the subjects. For instance, if an individual age 70 years was alive at entry into the study, then the individual was alive at the beginning of the aging process, that is, at age 65. As a consequence, the survival time considered by the standard method is shorter than the one used by the alternative approach. In our case, although the cohort was followed for 8 years, this was not enough time to estimate the median and the third quartile. Therefore, possible trends in the data for each level of functional capacity could not be observed. However, the alternative approach makes optimal use of the data by means of extending the follow-up time for each individual who enters into the study older than 65 years (Table 2). It is necessary to point out that the inferences reported by each method require different interpretation. The median computed using the standard approach describes the mor-

tality rate as a function of study duration, in this case the time elapsed since January 1986. On the other hand, because we are interested in studying mortality of the elderly population, the alternative approach provides the median age at death that was computed as a function of time since the onset of the elderly process (65 years). The medians under the alternative approach have a straightforward interpretation for a fixed covariate (e.g., gender), but they are interpreted as those obtained under stable conditions for a time-varying covariate (e.g., disability).

To overcome the problems mentioned for the standard approach, other authors have suggested building age-specific curves for each age group (7). This strategy is, however, less efficient than the use of the proposed time scale, because it reduces the information provided by age as a continuous variable. Other alternatives have also been proposed; for example, the computation of adjusted conditional probabilities of the event at each failure time (18), the average covariate method (18), and the corrected group prognosis (19,20).

Although it is necessary to break down the age group into categories for the estimation of the survival functions, this is not the case for the Cox regression. Specifically, in the regression setting one can use smaller age groups and even continuous terms if the association is linear. In doing so, one would obtain relative hazards of the exposure of interest adjusted by age as precise as in the alternative approach using age as the time scale. Indeed, we carried out the analysis using the standard approach with age as a continuous variable, and the relative hazards of disability were 1.77 and 1.96 for men and women, respectively. These values are very close to those obtained using the alternative approach. However, using age as an independent covariate with time-on-study as the time scale imposed a structure (e.g., logarithm of hazard is linear in age) that the alternative approach avoids because the underlying hazard of the Cox model with age as time scale is completely unrestricted (i.e., the nonparametric component of the regression approach).

Because data of studies of elderly adults are right-censored (i.e., some individuals are lost to follow-up or alive at the end of the study) and left-truncated (i.e., individuals entered into the study at different ages), an alternative, more appropriate methodology—namely, the extended-Kaplan-Meier estimator—was used. This estimator differs from the standard Kaplan-Meier estimator in that not all the subjects are considered at risk at time 0; that is, those individuals entering at age A_0 (older than 65) will not be included in the definition of the risk set for values $t < A_0$. Then, the covariables of each individual will contribute at the age that they have been recorded, and not before, avoiding the mixture of information of individuals who have different ages. This prevents the confounding effect of age.

Left-truncation is a situation characterized by the fact that the study cohort does not include those subjects who have not survived long enough to be observed. Consequently, the cohort that is observed is an incomplete sample (21,22). This fact must be taken into account in the statistical analysis. In fact, not including individuals who have previously died results in an underestimation of the mortality risk, because the individuals at the highest risk are not observed. To adjust or to compensate this bias, the survival analysis with delayed entry is needed (9). With large enough samples this estimator has similar properties to the standard product-limit estimator; that is, it is consistent and its distribution is approximately normal (23). However, the left-truncated approach is not free of difficulties. In studies where the sample size is small, there is the possibility that the survival estimator may be zero for some t_i , resulting in not having any individual at risk in a given moment. Then, the survival estimator becomes zero for some $t > t_i$. Approaches to avoid this problem are given by Lynden-Bell (24).

We have shown the advantages of using age as the time scale, and how to use methods of survival analysis for delayed entries to carry out estimation and regression analyses. Here, we have restricted our analysis to fixed covariates (e.g., gender), and time-varying covariates measured only at one time point (i.e., disability measured at baseline). Because disability is strongly related with age, it is possible that a person who is not disabled at baseline could become

disabled at a later age under follow-up; and by simply considering the disability at baseline, we will be biasing the comparison toward the null hypothesis. Even though we found strongly significant results using disability at baseline, it is important to incorporate the time-varying nature of disability, if available.

The methods presented here can naturally be extended, so as to partition each individual in as many individual periods corresponding to updates of the disability status. The records for the data analysis will contain: (a) the years after 65 an individual entered into a certain value of the disability status; (b) the years after 65 when that individual ceased to have that status; and (c) the vital status at the time the individual ceased to have that status (i.e., $\delta = 0$ if alive and move to another status, $\delta = 1$ if dead). In studies where updates of time-varying covariates are not available, it is recommended that total follow-up of an individual be restricted to a reasonable length of time when it is expected that the exposure will not likely change substantially.

It has been postulated that the importance of traditional risk factors, such as hypertension or smoking, tends to decrease with age. In the standard approach, this calls for the introduction of interactions between age and the risk factor of interest. In the alternative approach, because age is the time scale, this will correspond to a risk factor not fulfilling the usual assumption of proportional hazards in Cox regression. Therefore, in order to allow for a risk factor to have different levels of association with the outcome at different ages, all the methods developed to incorporate departures from proportional hazards are directly applicable to the alternative methods proposed here (25).

As we have shown, the alternative approach gives a more intuitively understandable interpretation of the survival curves, makes possible a juxtaposition of the available information, and indicates that age is the right time scale to build adequate inferences. In conclusion, we recommend the use of age as the time scale in the survival analysis when dealing with data from observational studies in elderly subjects.

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Appendix

Commands in S-plus, SAS, STATA, and EGRET

Using the notation introduced in the Methods section, W represents the years after 65 when an individual enters the study, T represents the years after 65 when an individual exits the study, and delta (δ) is the vital status of the individual at exit. Let X denote the disability variable (= 0 if no, = 1 if yes).

Estimation of the Survival Functions (Figure 3)

S-plus: plot(survfit(coxph(Surv(W,T,delta) ~ +strata(X))))
 SAS: proc phreg;
 model (W,T) * delta(0)=;
 strata X;
 baseline out=estimate survival=peralive;
 proc print;
 var T peralive X;
 STATA: stset T delta, t0(W)
 sts graph, by (X)
 EGRET: failure-time variable: T
 censoring indicator variable: delta
 entry-time variable: W
 stratify: X

Regression (Alternative Models in Table 3)

S-plus: summary(coxph(Surv(W,T,delta) ~ X))
 SAS: proc phreg;
 model (W,T)*delta(0)=X;
 STATA: stset T delta, t0(W)
 stcox X
 EGRET: definitions as in (I)
 regression terms: X