Efficacy of a Composite Biological Age Score to Predict Ten-Year Survival among Kansas and Nebraska Mennonites

MEREDITH UTTLEY[1,2] AND MICHAEL H. CRAWFORD[2]

Abstract In 1980 and 1981 Mennonite descendants of a group of Russian immigrants participated in a multidisciplinary study of biological aging. The Mennonites live in Goessel, Kansas, and Henderson, Nebraska. In 1991 the survival status of the participants was documented by each church secretary. Data are available for 1009 individuals, 177 of whom are now deceased. They ranged from 20 to 95 years in age when the data were collected. Biological ages were computed using a stepwise multiple regression procedure based on 38 variables previously identified as being related to survival, with chronological age as the dependent variable. Standardized residuals place participants in either a predicted-younger or a predicted-older group. The independence of the variables biological age and survival status is tested with the chi-square statistic. The significance of biological age differences between surviving and deceased Mennonites is determined by *t* test values. The two statistics provide consistent results. Predicted age group classification and survival status are related. The group of deceased participants is generally predicted to be older than the group of surviving participants, although neither statistic is significant for all subgroups of Mennonites. In most cases, however, individuals in the predicted-older groups are at a relatively higher risk of dying compared with those in the predicted-younger groups, although the increased risk is not always significant.

Barring disease and accidents, people age and, when old, die. Yet some people are perceived as old at age 50; others are perceived as young at age 70. Thus chronology, the elapsed time since birth, is not an effective measure of functional age. Instead, a measure of aging is needed that illuminates individual differences based on how well an organism functions compared with others of the same chronological age. People who function poorly are thought to be biologically older than their chronological peers. Conversely, people who function well might be deemed

[1]Division of Behavioral Sciences, Lander University, Greenwood, SC 29649.
[2]Laboratory of Biological Anthropology, Department of Anthropology, University of Kansas, Lawrence, KS 66045.

Human Biology, February 1994, v. 66, no. 1, pp. 121–144.

biologically younger. Ideally, a measure of functional-biological age would indicate a stage of aging free from chronological variability. Inherent in the concept of functional-biological age is the assumption that among a group of chronological peers those with greater biological age will be the first to die because they have reached a more advanced stage of aging sooner. If this is true, individuals who have higher functional age scores than their contemporaries should be overrepresented among the deceased in the future.

Our purpose here is to test the ability of functional-biological age computed using multiple regression to predict 10-year survival. Predictive ability is tested with three research questions. First, is the mean standardized residual, indicating biological age, higher for the group of deceased compared with surviving Mennonites? Second, are more biologically older individuals deceased than would be expected based on probability? Third, is the risk of being deceased higher for the functionally older? The null hypothesis is that predicted biological age is unrelated to 10-year survival.

Measuring Functional-Biological Age

The concept of biological age has been considered for nearly three decades, but agreement regarding method of measurement or evaluation of results has not been forthcoming. Various researchers have attempted to measure biological age using a variety of psychological or physiological tests. For example, Benjamin (1947) estimated biological age through a medical examination and life history questionnaire. Starting with a person's chronological age, years of equivalent age are added for hereditary and health risk conditions. This method is substantially subjective because most conditions can add a range of years, depending on their clinician-perceived seriousness. In contrast, Bell (1972) recommended estimating biological age according to a multiple regression formula. This formula provides an estimated age for each subject; the difference between the predicted and the actual age (residual) is then used as an indicator of biological age. This has been the most commonly applied method in physiology studies [e.g., Durbina et al. (1984), Furukawa et al. (1975), Ries and Pöthig (1984), Voitenko and Tokar (1983), and Webster and Logie (1976)].

Borkan (1978) developed a univariate residual technique for studying interindividual variation in aging. This method requires that each variable be regressed separately against chronological age. The standardized residuals of all the regressed variables are computed for each subject and are retained for further analysis. Thus each subject has a biological age profile (BAP), which consists of a residual score for each

variable included in the profile. Based on each residual score, a subject is viewed as being either biologically older or younger than others of the same chronological age with regard to each variable. Each subject has a number of biological ages, which is equal to the number of variables in the profile.

Both the univariate and the multivariate methods provide measures of age status or function relative to one's chronological peers. Beyond that, however, the methods are quite different. With stepwise multiple regression, variables enter the equation based on their correlation with the dependent variable and the remaining independent variables. Thus, if several independent variables are highly correlated, only one is expected to enter the equation, even if the variables measure different elements of a single physiological component. Only with multivariate analyses are the interactions within a group of independent variables considered. These interactions, however, can complicate the interpretation of the results. Although variable interactions are omitted from univariate analyses, more than one element of a single component may be significant. For example, the significance of different but related measures of lung function would highlight the importance of the whole physiological component. Uttley (1991) demonstrated that multivariate and univariate analyses focusing on variables related to survival provide similar results. A common problem exists with either the univariate or the multivariate approach. In both methods chronological age is used as the dependent variable, but it is chronological age that researchers hope to replace.

Tests of Biological Age. Four groups of researchers have compared predicted ages for healthy groups to the predicted ages for unhealthy groups to test the relevance of the concept of biological age. From an original sample of 1080 apparently well females, Webster and Logie (1976) selected 97 nonsmokers (9%) who were judged to be healthiest. Predicted ages for this group of women were significantly less (1.5 years) than actual ages ($p < 0.02$). For the 51 women of this group who also rated their health as being good, the mean predicted age was 2.6 years less than actual age ($p < 0.005$). Predicted ages for the 12 women who, regardless of the observer's evaluations, considered their health to be poor, were higher than actual ages; however, the discrepancy was not significant.

Furukawa et al. (1975) compared 111 normotensive individuals with 65 hypertensive individuals (31 females, 34 males) and found that predicted ages for the hypertensive group were significantly higher than actual ages (p not given).

Borkan (1978) compared the mean biological age profiles for several health-based subgroups of participants. Smokers compared with nonsmokers exhibited reduced lung function (equivalent to being bio-

logically older), but the difference was not significant. The 15% of individuals with high Cornell Medical Index scores ($\geq$19) (least healthy) compared with the 15% of those with low index scores (healthiest) exhibited significantly "older" lung function, plasma glucose, and neuromuscular performance. Individuals diagnosed as having cardiovascular disease compared with those free of the disease were significantly older with respect to systolic blood pressure, plasma glucose, and neuromuscular performance.

Among subjects studied by Facchini et al. (1992), smokers also exhibited significantly reduced lung function (biologically older) and wine drinkers compared with nondrinkers exhibited "older" levels of plasma glucose and cholesterol, but these differences were not significant.

It is encouraging that the predicted ages are, in fact, higher for persons from unhealthy groups. One would expect unhealthy individuals to demonstrate decreased function, but biological age is intended to indicate different stages of aging, not just to correlate with diminished function. Thus these health comparisons do not go far enough. If predicted biological ages are accurate, those judged to be older than their chronological peers would die sooner than those peers. Whether or not computed functional-biological age scores are predictive of mortality, however, has rarely been considered.

Tests of Survival. Borkan (1978) compared the mean biological age profile for survivors with that for deceased using Student's *t* tests. Before they died, the deceased exhibited significantly poorer lung function, higher systolic blood pressure, reduced neuromuscular performance, and lower levels of serum albumin and globulin ($p \leq 0.05$).

Uttley (1991) followed Borkan's method of univariate analysis to compare surviving and deceased Mennonites. Before they died, deceased women showed markedly higher serum levels of blood urea nitrogen and creatinine and lower levels of albumin and total iron. They also exhibited higher diastolic blood pressure, poorer lung function, and diminished neuromuscular performance and trunk flexibility and rated their health as being poorer. Before they died, deceased men showed markedly higher serum levels of blood urea nitrogen (BUN) and uric acid, and an elevated BUN/creatinine ratio but lower levels of albumin. They exhibited higher diastolic blood pressure and diminished neuromuscular performance and trunk flexibility and rated their health as being poorer.

Botwinick et al. (1978) identified a battery of eight tests, including cognitive, psychomotor, personality, and health-related measures, that correctly classifies 68% of subjects with respect to their survival status (alive or deceased) in the succeeding five years. For all psychological tests the relationship between performance and survival is small (Botwinick 1984). Tests of verbal skills worked best for predicting survival

within a five-year time span (Botwinick 1984; Jarvik and Falek 1963). Steuer et al. (1981) found that survival predictive ability was best for subjects under age 65. With a 25-year follow-up of subjects, Palmore (1982) found that such nonverbal tests as self-rated health, subjective physical function rating, and work or health satisfaction were the best predictors of survival. Jarvik and Falek (1963) were among the first to report on the theory of terminal drop or decline, which holds that cognitive functional decline is more closely related to death than to chronological age. Nothing comparable to terminal drop has been identified in physiology studies. This would require longitudinal research.

Three groups of researchers have found self-rated health status to be correlated with survival. LaRue et al. (1979) divided subjects into two age groups: 77–84 years and 85–93 years. For the younger group only, both self-rated and objective health were correlated significantly with five-year survival ($p < 0.005$). Kaplan et al. (1988) found a strong inverse relationship between personal health rating and five-year survival. Idler and Angel (1990), in a 12-year follow-up to the National Health and Nutrition Examination Survey (NHANES-1), also found that mortality risks were negatively correlated with self-rated health status. In particular, for men who initially rated their health as poor, only 60% survived through the follow-up period. Yet among women who rated their health as poor nearly 80% survived the 12 years.

Materials and Methods

Study Population. The data reported here were collected during research conducted more than a decade ago (1980–1981) when Mennonite residents of Goessel, Kansas, and Henderson, Nebraska, participated in a multidisciplinary project conducted by researchers from the University of Kansas and sponsored by the National Institute on Aging (Crawford and Rogers 1982). Community members are descendants of a group that immigrated to the United States from the Ukraine in 1874. Mennonites have generally preserved their separate genetic and sociocultural identity and thus constitute an identifiable population for study. For the convenience of participants, data collection clinics were held at each church. Clinic attendees represented approximately 50% of the community adults (Devor and Crawford 1984; Devor et al. 1986). Although participants ranged in age from 20 to 90 years, the individuals aged 50 and above (365 women and 296 men) are the focus of this research. Eighty-six women and 91 men have subsequently died (as of 1991). Among these individuals, the earliest death from natural causes occurred at age 57. Six individuals whose deaths were accidental have been excluded from analysis. Tobacco is not used and wine is used rarely. Thus our data are

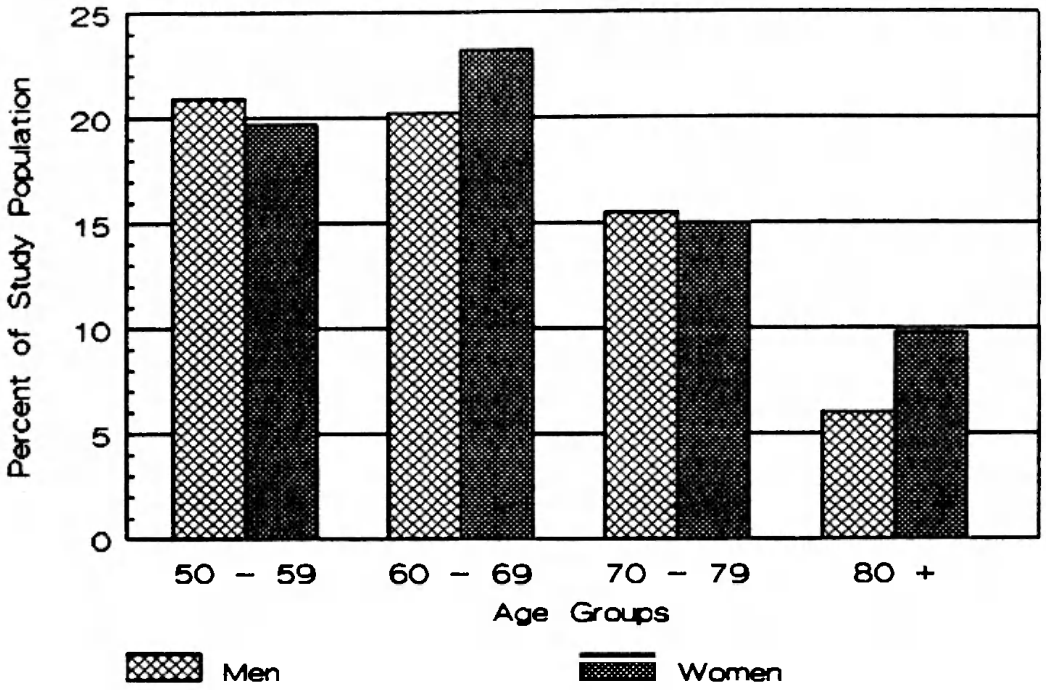

Figure 1. Size of age groups as a percentage of the Midwest Mennonite study population.

not confounded by these covariates. Figure 1 shows the age structure of the Midwest Mennonite study population. Among both women and men, approximately 20% were in their fifties and 15% were in their seventies. About 23% of women and 20% of men were in their sixties. About 10% of women and 6% of men were in their eighties.

One-way analyses of variance demonstrate significant sex differences for most variables. Consequently, the women and men were analyzed separately in this study. Lifestyles remain similar among residents of Goessel and Henderson, but the original settlement pattern suggests the presence of some founder effect (Uttley 1991). Uttley (1991) identified variables that predict survival for at least one subsample of Mennonites. Five physiological components (serum protein, lipids, electrolytes, metabolic wastes, and body morphology) were represented. The predictive variables within a component, however, were specific to either females or males. Besides variables from the five components, total iron, hand steadiness, and reaction time were used as predictors for women. Glucose, diastolic and systolic blood pressure, movement time, and self-rated health were used as predictors for men. In the current research the variables were combined in multivariate analyses to generate a composite biological age score for each subject.

Available Data. Data collected among the Mennonites included variables used in other studies of biological age, body morphology, and blood

chemicals typically used to assess clinical dysfunction and disease. Participants completed health history forms and were examined by a physician. Blood pressure, anthropometric, and blood chemistry data were collected in both communities. In addition, in Goessel, lung function, neuromuscular performance, trunk flexibility, and grip strength were measured. In Henderson self-rated health was added to the original data set. Thus two sets of predictive variables were available for each subgroup of Mennonites. One set includes only those variables collected in both Goessel and Henderson clinics (referred to as common community variables). The second set includes the first set and adds the variables collected in either Goessel or Henderson to the appropriate community subgroups (referred to as community-specific variables). Analyses of the pooled Goessel and Henderson (Midwest Mennonite) samples are limited to the common community variables.

The variables used in this research were selected from the original set because of their association with survival demonstrated by Uttley (1991). In that research Uttley regressed individual variables against chronological age. For individuals aged 50 and older, the variables showed linear relationships with age, although for some variables the change across the age span was slight. Our selection of variables follows Brown and Forbes's (1976) call for an index of biological age that reflects the association of mortality and chronological age and Costa and McCrae's (1977) call for variables that have been documented to have a linear relationship with chronological age. The variables available for the current analyses and the direction of their linear relationship with chronological are shown in Table 1. For 12 variables the linear relationship with chronological age is different for women and men. Most of those variables assess serum lipids and electrolytes or body morphology. These sex differences will be examined in depth in future research.

Analytical Methods. Using stepwise multiple regression analyses, we predicted an age for each clinic participant. Because the predicted age is based on each person's functional status relative to other individuals of the same chronological age, the predicted age is used to represent functional-biological age. The difference (error) between the chronological age and the predicted age (residual) is standardized and retained for analyses. Standardized residuals represent a normally distributed data sample from a population. Persons with negative residuals (less than 0) are predicted to be younger than their chronological ages whereas persons with positive residuals (greater than 0) are predicted to be older. Individuals are divided into four groups based on predicted functional age (younger, older) and survival status (alive, deceased).

Our research questions were tested using a variety of statistical techniques. Testing the difference between the mean predicted ages

Table 1. Variables Available for Testing the Relationship of Functional-Biological Age and Survival among Mennonite Participants from Kansas and Nebraska

	Relationship with Age[a]			
Variable	*Females*	*Males*	*Kansas*[b]	*Nebraska*[b]
Body mass index	↓	↓	+	+
Triceps	↓	↑	+	+
Sum of skinfolds	↓	↑	+	+
Glucose	↑	↑	+	+
Hemoglobin	↑	↓	+	+
Albumin	↓	↓	+	+
Globulin	↑	↑	+	+
T_4	↓	↑	+	+
Total protein	↓	↓	+	+
Albumin/globulin ratio	↓	↓	+	+
Uric acid	↑	↑	+	+
Blood urea nitrogen (BUN)	↑	↑	+	+
Creatinine	↑	↑	+	+
BUN/creatinine ratio	↑	↑	+	+
Triglycerides	↑	↑	+	+
Cholesterol	↑	↓	+	+
High-density lipoprotein (HDL)	↓	↑	+	+
Low-density lipoprotein	↑	↓	+	+
Cholesterol/HDL ratio	↑	↓	+	+
Calcium	↓	↓	+	+
Potassium	↓	↑	+	+
Sodium	↓	↑	+	+
Chloride	↓	↓	+	+
Phosphorus	↓	↓	+	+
Alkaline phosphatase	↑	↑	+	+
AST (SGOT)[c]	↑	↓	+	+
Total iron	↓	↓	+	+
Systolic blood pressure	↓	↓	+	+
Diastolic blood pressure	↑	↑	+	+
Forced expiration volume	↓	↓	+	–
Vital capacity	↓	↓	+	–
Reaction time	↑	↑	+	–
Movement time	↑	↑	+	–
Grip strength	↓	↓	+	–
Hand/eye coordination	↓	↓	+	–
Hand steadiness	↓	↓	+	–
Trunk flexibility	↓	↓	+	–
Self-rated health	↑	↓	–	+

a. An arrow pointing downward indicates that the variable decreases with increasing chronological age. An arrow pointing upward indicates that the variable increases with increasing chronological age.

b. A plus sign indicates that the data were collected; a minus sign indicates that data were not collected.

c. AST, asparate aminotransferase; SGOT, oxaloacetic transaminase.

(functional residuals) for survivors and deceased constitutes a Model 1 two-sample analysis of variance. A t test is the traditional method of solving such a comparison of two means. With infinite degrees of freedom, a t test value is equivalent to the square root of F. The t distribution, however, allows for the small numbers in the groups of deceased. From the null hypothesis, we expect that $X_{\text{alive}} - X_{\text{deceased}} = 0$. It is the deviation of the difference from 0 that is being tested by the t statistic (Sokal and Rohlf 1981).

The chi-square statistic (χ^2) is used to test the independence of functional age scores and 10-year survival. In a contingency table each cell has an expected n based on a priori knowledge or on normal probability determined from the row and column marginal totals. For this research each expected cell n is computed as (row total $\times$ column total)/table total. If the row and column variables are independent, $n_{\text{obs}} = n_{\text{expected}}$. The chi-square statistic tests the deviation of the observed cell frequencies from the expected cell frequencies. It is computed as

$$\chi^2 = \sum \frac{(O - E)^2}{E}, \tag{1}$$

where O is the observed frequency and E is the expected frequency. For the 2 $\times$ 2 tables used in this research, chi-square significance is based on 1 degree of freedom (Sokal and Rohlf 1981).

The risk ratio is used to test whether subjects who are functionally older than their contemporaries are more likely to have died. As with the chi-square statistical analyses, clinic participants are divided into groups based on their functional age score and their survival status. If the two variables are independent, the deceased would be equally divided between those who are functionally younger and those who are functionally older. A perfect correspondence between the two variables would find all the deceased among the functionally older group. A risk ratio is a comparison of the proportion of the deceased who are in each functional group. The ratio is computed as

$$\frac{\text{number of older deceased}}{\text{number biologically older}} \Big/ \frac{\text{number of younger deceased}}{\text{number biologically younger}} = \text{risk ratio}. \tag{2}$$

A result greater than 1 indicates that subjects with functional ages older than those of their chronological peers experience a higher risk of dying (Mausner and Kramer 1985).

Given the accuracy of the assertion that for a middle-aged person advancing age statistically increases the probability of death (Waring 1978), two logical expectations follow. First, the linear relationship (regression) between any given variable and chronological age will be consistent with

the regression based on the subset of participants who are now deceased. Thus functional ages, based on standardized residuals, are expected to be higher for deceased participants and lower for survivors. Second, those individuals who are estimated to be biologically or functionally older than their calendar years are expected to be at greater risk of dying than their chronological peers.

Results

Regression Analyses. Using variables collected in both Mennonite communities in stepwise multiple regression analyses, we predicted functional ages for clinic participants. Table 2 lists the variables included in the regression equations for the pooled samples of women and men. For both women and men, the variables relate to blood pressure, serum proteins, lipids, and metabolic wastes. Metabolic wastes are more important for women than for men. Lipids are more important for men. In addition, body morphology enters the equation for women and electrolytes enter the equation for men. By using the same variables but analyzing each town separately, we found that blood pressure and metabolic wastes enter all equations for both sexes. Body morphology measures enter the equations for Henderson participants and Goessel women; lipid measures enter the equations for Goessel participants, and electrolytes enter the equation for Goessel men. The relative importance of the variables differ by group, however. Table 3 lists the common community variables included in the regression equations when the women and men from each town are examined separately.

In Goessel variables measuring neuromuscular performance, lung function, strength, and trunk flexibility were collected in addition to the basic set of common community variables. Table 4 lists the community-specific variables included in the regression equations for Goessel participants. For both sexes grip strength is the first variable to enter the regression equation; forced expiratory volume and trunk flexibility also enter, and the importance of metabolic wastes is reduced. Among women movement time (RT-CNS) enters the equation; among men reaction time enters the equation. For both sexes the entrance of community-specific variables alters the importance of other types of variables. Among women the importance of serum proteins increases and the importance of body morphology and lipids decreases. Among men the importance of serum proteins and blood pressure decreases and the importance of body morphology and lipids increases. For both sexes, adding neuromuscular performance, lung function, strength, and trunk flexibility increases the R^2 values and the number of variables included in the regression equation. For both groups the increase in the number of variables leads to a de-

the regression based on the subset of participants who are now deceased. Thus functional ages, based on standardized residuals, are expected to be higher for deceased participants and lower for survivors. Second, those individuals who are estimated to be biologically or functionally older than their calendar years are expected to be at greater risk of dying than their chronological peers.

Results

Regression Analyses. Using variables collected in both Mennonite communities in stepwise multiple regression analyses, we predicted functional ages for clinic participants. Table 2 lists the variables included in the regression equations for the pooled samples of women and men. For both women and men, the variables relate to blood pressure, serum proteins, lipids, and metabolic wastes. Metabolic wastes are more important for women than for men. Lipids are more important for men. In addition, body morphology enters the equation for women and electrolytes enter the equation for men. By using the same variables but analyzing each town separately, we found that blood pressure and metabolic wastes enter all equations for both sexes. Body morphology measures enter the equations for Henderson participants and Goessel women; lipid measures enter the equations for Goessel participants, and electrolytes enter the equation for Goessel men. The relative importance of the variables differ by group, however. Table 3 lists the common community variables included in the regression equations when the women and men from each town are examined separately.

In Goessel variables measuring neuromuscular performance, lung function, strength, and trunk flexibility were collected in addition to the basic set of common community variables. Table 4 lists the community-specific variables included in the regression equations for Goessel participants. For both sexes grip strength is the first variable to enter the regression equation; forced expiratory volume and trunk flexibility also enter, and the importance of metabolic wastes is reduced. Among women movement time (RT-CNS) enters the equation; among men reaction time enters the equation. For both sexes the entrance of community-specific variables alters the importance of other types of variables. Among women the importance of serum proteins increases and the importance of body morphology and lipids decreases. Among men the importance of serum proteins and blood pressure decreases and the importance of body morphology and lipids increases. For both sexes, adding neuromuscular performance, lung function, strength, and trunk flexibility increases the R^2 values and the number of variables included in the regression equation. For both groups the increase in the number of variables leads to a de-

Table 3. Common Community Variables Included in the Stepwise Multiple Regression Computation of Biological Age for Mennonite Men and Women[a]

Variable Entered	*b*	*SE of b*	*β*	*N*	*RMS*	*r BA/CA*
Goessel women, age 50 and older						
Blood urea nitrogen (BUN)	0.39	0.15	0.18	120	26.2	0.7571
Albumin	−20.44	3.69	−0.48			
Diastolic blood pressure	0.16	0.05	0.28			
Hemoglobin	1.57	0.62	0.18			
Low-density lipoprotein	0.14	0.07	0.55			
Calcium	2.45	1.71	0.12			
Systolic blood pressure	−0.16	0.11	−0.12			
Skinfold sum	−0.25	0.03	−0.62			
Triglycerides	0.01	0.01	0.12			
Uric acid	1.75	0.74	0.20			
T_4	−0.57	0.46	−0.08			
Cholesterol	−0.09	0.06	−0.33			
Potassium	1.34	0.85	0.11			
Phosphorus	−2.21	1.74	−0.09			
Henderson women, age 50 and older						
Diastolic blood pressure	0.13	0.03	0.37	164	18.2	0.5407
Systolic blood pressure	−0.17	0.07	−0.21			
Phosphorus	−1.58	1.24	−0.09			
Total iron	−0.02	0.02	−0.09			
BUN/creatinine ratio	0.50	0.14	0.24			
Uric acid	1.20	0.53	0.18			
Skinfold sum	−0.10	0.03	−0.30			
Body mass index	0.09	0.04	0.24			
AST (SGOT)[b]	0.15	0.13	0.08			
Calcium	−2.69	1.71	−0.12			
Goessel men, aged 50 and older						
Diastolic blood pressure	0.22	0.05	0.38	130	22.5	0.6526
Albumin	−9.40	3.83	−0.21			
Blood urea nitrogen	0.42	0.16	0.21			
Systolic blood pressure	−0.31	0.11	−0.27			
Chloride	−0.72	0.27	−0.20			
Potassium	2.78	1.08	0.19			
Phosphorus	−0.361	1.93	−0.15			
Cholesterol	−0.03	0.02	−0.14			
Uric acid	0.99	0.60	0.13			
Glucose	0.04	0.03	0.11			
Albumin/globulin ratio	−4.56	3.99	−0.10			
Henderson men, age 50 and older						
Systolic blood pressure	−0.27	0.08	−0.30	136	19.3	0.5628
Diastolic blood pressure	0.13	0.04	0.28			
Creatinine	4.66	2.60	0.14			
Potassium	1.38	0.61	0.17			
Triceps	0.51	0.20	0.26			
Alkaline phosphatase	0.04	0.03	0.13			
Glucose	0.03	0.02	0.14			
AST (SGOT)[b]	−0.14	0.10	−0.11			
Body mass index	−0.07	0.05	−0.14			

a. *N* is the number of participants on which the regression equation is computed. RMS is the root mean square, which is the best estimate of the pooled standard error. BA is biological age; CA is chronological age. Variables listed in the order in which they were entered into the equation.

b. AST, asparate aminotransferase; SGOT, oxaloacetic transaminase.

Table 4. Goessel Community Variables Included in the Stepwise Multiple Regression Computation of Biological Age for Kansas Mennonites[a]

Variable Entered	*b*	*SE of b*	*β*	*N*	*RMS*	*r BA/CA*
Women, age 50 and older						
Grip strength	−0.47	0.10	−0.31	98	26.0	0.9181
Blood urea nitrogen	0.15	0.10	0.07			
Phosphorus	−3.44	1.18	−0.14			
Systolic blood pressure	−0.25	0.07	−0.19			
Diastolic blood pressure	0.13	0.03	0.22			
Hemoglobin	0.96	0.42	0.11			
Low-density lipoprotein	0.12	0.04	0.46			
Globulin	7.09	3.35	0.27			
Movement time	9.70	2.96	0.16			
Albumin	−12.78	3.79	−0.30			
Skinfold sum	−0.13	0.02	−0.32			
Trunk flexibility	−0.44	0.16	−0.13			
Potassium	1.21	0.58	0.10			
Albumin/globulin ratio	12.73	7.05	0.26			
T_4	−0.58	0.31	−0.08			
Calcium	1.37	1.23	0.07			
Forced expiratory volume	−0.00	0.00	−0.23			
Cholesterol	−0.06	0.04	−0.24			
Uric acid	0.61	0.50	0.07			
Men, age 50 and older						
Grip strength	−0.27	0.07	−0.28	92	20.2	0.9019
Forced expiratory volume	−0.00	−0.00	−0.31			
Reaction time	22.41	5.65	0.24			
T_4	1.09	0.32	0.19			
Glucose	0.05	0.02	0.14			
Uric acid	0.46	0.45	0.06			
Skinfold sum	−0.11	0.05	−0.16			
Diastolic blood pressure	0.06	0.03	0.10			
Albumin	−7.00	2.65	−0.16			
Trunk flexibility	−0.49	0.19	−0.14			
Total iron	0.03	0.02	0.10			
Chloride	−0.62	0.23	−0.18			
Cholesterol	−0.05	0.02	−0.19			
Cholesterol/HDL ratio	1.02	0.44	0.19			
Potassium	1.26	0.78	0.09			
Body mass index	0.07	0.05	0.11			
Alkaline phosphatase	−0.03	0.02	−0.07			
Hand steadiness	−0.07	0.05	−0.09			
AST (SGOT)[b]	0.17	0.12	0.08			
Creatinine	3.77	2.58	0.09			
Triglycerides	−0.01	0.01	−0.09			
Sodium	0.28	0.27	0.07			

a. *N* is the number of participants on which the regression equation is computed. RMS is the root mean square, which is the best estimate of the pooled standard error. BA is biological age; CA is chronological age. Variables listed in the order in which they were entered into the equation.

b. AST, asparate aminotransferase; SGOT, oxaloacetic transaminase.

Table 5. Henderson Community Variables Included in the Stepwise Multiple Regression Computation of Biological Age for Nebraska Mennonites[a]

Variable Entered	*b*	*SE of b*	*β*	*N*	*RMS*	*r BA/CA*
Women, age 50 and older						
Diastolic blood pressure	0.13	0.04	0.36	165	15.5	0.5328
Systolic blood pressure	−0.18	0.09	−0.22			
Phosphorus	−1.86	1.49	−0.11			
Albumin	−3.90	3.35	−0.10			
Total iron	0.02	0.02	−0.09			
BUN/creatinine ratio	0.47	0.18	0.23			
Uric acid	1.08	0.65	0.16			
Skinfold sum	−0.09	0.04	−0.30			
Body mass index	0.09	0.05	0.23			
Men, age 50 and older						
Rated health	−3.06	1.07	−0.27	90	16.3	0.6133
Diastolic blood pressure	0.15	0.05	0.33			
Systolic blood pressure	−0.23	0.09	−0.26			
Triceps	0.38	0.18	0.20			
Potassium	1.45	0.77	0.18			
Creatinine	4.41	3.04	0.13			
Hemoglobin	−0.73	0.57	−0.12			
Phosphorus	−1.37	1.10	−0.12			
AST (SGOT)[b]	−0.14	0.11	−0.12			
Alkaline phosphatase	0.04	0.03	0.10			

a. *N* is the number of participants on which the regression equation is computed. RMS is the root mean square, which is the best estimate of the pooled standard error. BA is biological age; CA is chronological age. Variables listed in the order in which they were entered into the equation.

b. AST, asparate aminotransferase; SGOT, oxaloacetic transaminase.

able to enter the regression equation. With its addition, the importance of body morphology decreases, but the rest of the variables change only slightly. The R^2 value increases substantially.

Of the Mennonites who attended church clinics, the participants who subsequently died were, on average, older than the survivors. One-way analyses of variance demonstrate that mean functional residuals increase with increasing age for participants; however, the variances associated with the residuals do not differ significantly between age groups. Figure 2 shows the range of the functional residuals by sex, community, and age group. The residuals range from −2.35 to 0.56 for 50–59-year-olds, from −1.8 to 2.21 for 60–69-year-olds, from −1.57 to 2.3 for 70–79-year-olds, and from 0 to 2.98 for 80–89-year-olds.

For both sexes the distributions of residuals for survivors and deceased overlap, although the means of the distributions for the deceased are shifted upward slightly. The distribution for women ranges from −2.4

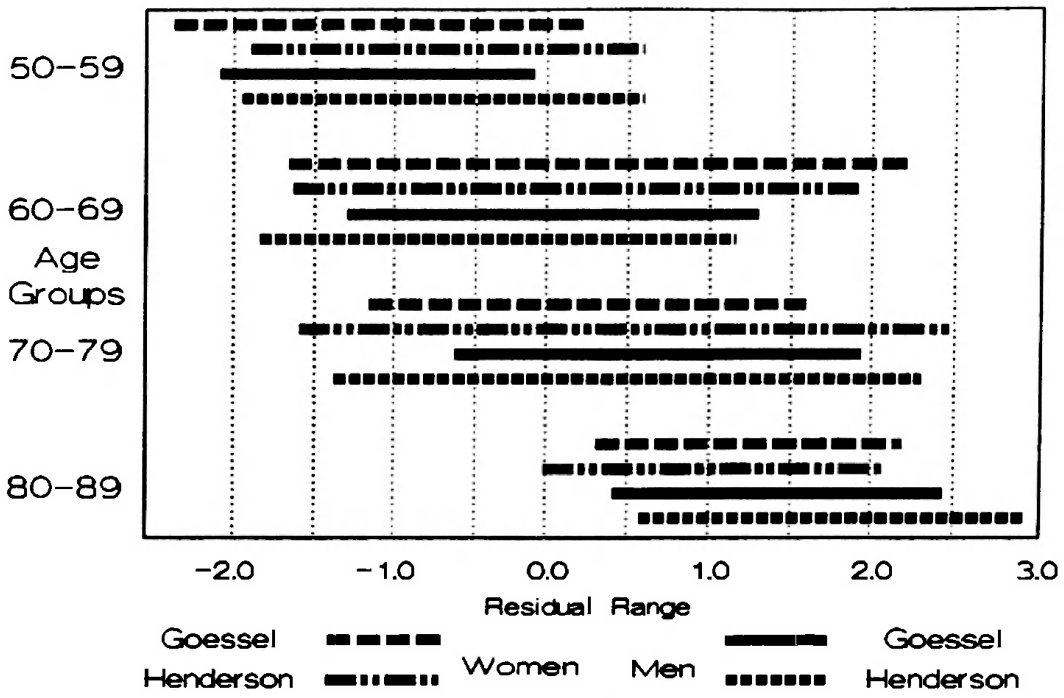

Figure 2. Ranges for functional age residual scores for Midwest Mennonites using variables collected in both Goessel, Kansas, and Henderson, Nebraska.

to 2.5 for survivors and from −2.2 to 2.1 for deceased. The distribution for men ranges from −2.1 to 2.7 for survivors and from −1.8 to 2.9 for deceased. Figure 3 shows the distribution of functional residual scores, by sex, for surviving and deceased Mennonites.

***t* Test Analyses.** Do data collected a decade ago indicate that subsequently deceased individuals were functionally older than their surviving counterparts? With one exception, mean predicted ages for groups of deceased are higher than those for groups of survivors. By using variables common to both towns, we found that differences between mean predicted ages are significant for Henderson women, Goessel and Henderson men, and pooled women and men. With variables specific to each town, differences are significant only for Henderson participants. Mean functional age residuals are listed by variable set, town, sex, and survival status in Table 6.

With the inclusion of Goessel-specific variables, higher R^2 values are generated from the multiple regression analyses; however, these higher R^2 values do not result in more significant differences between survivors and deceased. For surviving women the mean predicted age residual and standard deviation increase slightly. For deceased women, however, the mean predicted age decreases substantially and the standard deviation increases slightly. The deceased have a lower mean predicted age. These

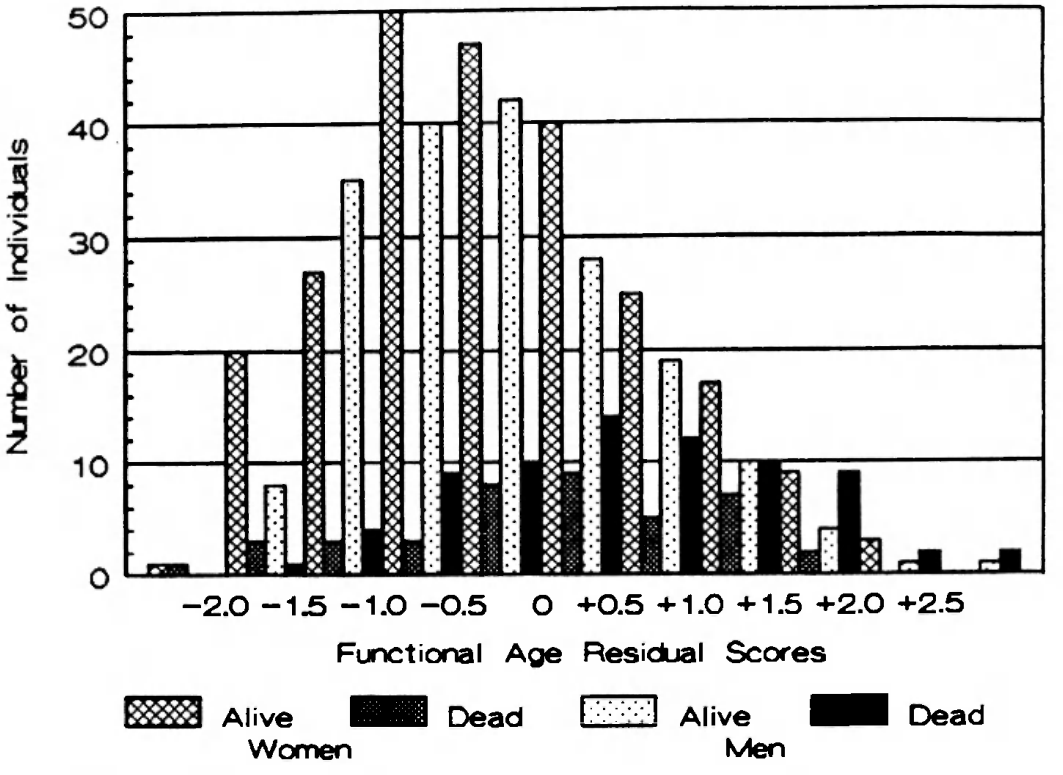

Figure 3. Standardized functional age residuals for surviving and deceased Midwest Mennonites. Variables included in the computation were collected in both Henderson and Goessel.

changes make the two groups less alike, but in a direction opposite to that expected. The increased dissimilarity leads to a greater significance for the relationship between the two groups. Among Goessel men the mean predicted age for survivors increases slightly and the standard deviation decreases slightly. For the deceased the mean predicted age decreases, but the standard deviation increases substantially. As a result, the relationship between the two groups becomes less significant.

For Henderson women, adding the variable self-rated health leaves the R^2 value and the significance level basically unchanged. For survivors the mean predicted age increases slightly and the standard deviation decreases. Among the deceased both the mean predicted age residual and the standard deviation decrease. For both groups of Henderson men the mean predicted age and the standard deviation decrease. The significance level also decreases, although the R^2 value increases.

Chi-Square Analyses. Are functionally older individuals overrepresented among the subsequently deceased? Participants were assigned to cells of a contingency table based on their relative age residual (younger, older) and their survival status (alive, dead). The null hypothesis (H_0)

Table 6. *t* Test Comparison of Standardized Age Residuals for Surviving and Deceased Mennonites

	Variables Common to Both Towns			*Variables Specific to Each Town*		
Group	*N*	*Residual Mean ± SD*	*Significance*	*N*	*Residual Mean ± SD*	*Significance*
Goessel						
Women						
Alive	95	−0.308 ± 1.002	0.918	81	−0.259 ± 1.210	0.085
Deceased	25	−0.284 ± 1.096		17	−0.826 ± 1.292	
Men						
Alive	88	−0.354 ± 0.894	0.000	69	−0.224 ± 0.889	0.054
Deceased	40	0.528 ± 0.809		22	0.200 ± 0.881	
Henderson						
Women						
Alive	144	−0.088 ± 0.963	0.006	145	−0.084 ± 0.953	0.007
Deceased	19	0.578 ± 0.962		19	0.553 ± 0.949	
Men						
Alive	101	−0.213 ± 0.863	0.000	69	−0.227 ± 0.825	0.010
Deceased	35	0.569 ± 1.067		20	0.332 ± 0.914	
Pooled						
Women						
Alive	239	−0.220 ± 0.923	0.056			
Deceased	41	0.082 ± 0.986				
Men						
Alive	188	−0.280 ± 0.874	0.000			
Deceased	73	0.531 ± 1.033				

that predicted functional age is unrelated to 10-year survival was tested using the chi-square statistic. Table 7 shows the relative age classifications, survival status, and chi-square value for each population subgroup. Both variable sets are included. Based on variables collected in both communities, H_0 can be rejected for men from both Goessel and Henderson, for the pooled male sample, and for women from Henderson. By adding community-specific variables to the computation, we found that H_0 can be rejected for Henderson women and men but not for Goessel participants. Thus an older relative age does not always separate survivors from deceased.

Risk Analyses. For Goessel women, using community-specific variables, those who are functionally older experience a lower risk of mortality than those who are functionally younger. For all other subgroups, however, biologically older individuals are at greater risk of dying than are biologically younger individuals, although the risk ratio is not always significant. Table 8 lists the risk ratio and significance for each population subgroup. Both variable sets are included.

Table 7. Chi-Square Statistic for Testing the Independence of Predicted Age and Survival Status among Mennonites

	Common Variables[a]			*Specific Variables*[b]		
Group	*Alive*	*Dead*	χ^2	*Alive*	*Dead*	χ^2
Goessel						
Women						
Younger	62	12	0.100	48	14	0.073
Older	32	13		33	3	
Men						
Younger	58	10	0.000	41	10	0.251
Older	30	30		28	12	
Henderson						
Women						
Younger	82	4	0.003	84	4	0.002
Older	62	15		61	15	
Men						
Younger	61	11	0.003	46	6	0.003
Older	40	24		23	14	
Pooled samples						
Women						
Younger	145	19	0.080			
Older	93	22				
Men						
Younger	125	24	0.000			
Older	63	49				

a. Variables collected in both the Goessel and the Henderson clinics.
b. Variables collected in either the Goessel or the Henderson clinic.

Discussion

Our decision to include only those individuals who were at least 50 years old when they attended the church clinics is based on a review of the pertinent literature. Borkan et al. (1982) and Strehler (1977) discuss aging as primarily occurring in the postreproductive period. Handler (1970) stresses the deterioration of a mature organism resulting from time-dependent, essentially irreversible changes. Waring (1978) focuses on midlife as his point of orientation, because the probability of death increases at that point. Botwinick (1981) believes that the more groups we divide research samples into, the more we will learn about the aging process. He suggests using 10-year cohorts beginning at age 55. Kohn (1971) states that research should begin at maturity, when aging is continuous and irreversible. Analyses of those participants who were at least 50 years old focuses on those ages when death becomes increasingly likely. Among the Midwest Mennonites, this age limit omitted only two of the deceased individuals from the study cohort.

Table 8. Older/Younger Risk of Death Ratio among Midwest Mennonites

Group	*Common Variables*[a]	*Specific Variables*[b]
Goessel		
Women	1.8 (NS)	0.37 (NS)
Men	3.4[d]	1.5 (NS)
Henderson		
Women	4.2[c]	4.3[c]
Men	2.5[c]	3.3[c]
Pooled		
Women	1.7 (NS)	
Men	2.7[d]	

a. Variables collected in both the Goessel and the Henderson clinics.
b. Variables collected in either the Goessel or the Henderson clinic.
c. $p < 0.01$.
d. $p < 0.001$.
NS: $p > 0.05$.

It is apparent that no consistent relationship between predicted functional age and 10-year survival has been demonstrated for subgroups of Kansas and Nebraska Mennonites using a stepwise multiple regression technique. Several possible reasons should be considered. First, the regression technique uses chronological age as the dependent variable. Thus the stepwise procedure maximizes the fit between predicted functional age and chronological age to obtain the highest possible R^2 values. Researchers of biological age desire to uncover a set of universal stages in aging that allows for the evident variability in the chronological timing of each stage. The use of chronological age as the reference point, however, may inhibit the realization of this goal. It can be seen in Figure 2 that for all subgroups of Mennonites the age residual ranges parallel the increase in chronological age. Thus the effect of chronological age has not been fully removed. In fact, the higher the correlation between the regression equation and the chronological age, the greater the remaining effect of chronology. The confounding effect of chronological age with regression analyses has been a concern since it was discussed by Costa and McCrae (1977). This confounding of chronology remains, even when the independent variables in the regression are chosen, as in this research, because of their ability to predict mortality.

Second, it is likely that some variables related to chronological age or functional ability are not related to survival. With the addition of strength, neuromuscular performance, and lung function, the variables found most consistently in other studies of biological age, the Goessel variable set explains a greater proportion of the variance associated with chronological age. The ability of the variable set to segregate survivors

from deceased does not improve, however. Voitenko and Tokar (1983) suggested that with variables correlated with chronological age the resulting predictive functions may actually be unrelated to survival. Hearing threshold was their most informative variable, yet it is largely insignificant with respect to age-dependent mortality. The Goessel equations are also consistent with Brown and Forbes's (1976) finding that lipofuscin concentration, which increases with age, does not appear to lead to a higher risk of death for groups with higher concentrations. The work of Clarkson (1978), Spirduso (1975), and Spirduso and Clifford (1978) suggests that reaction time variables may be more highly correlated with regular activity level than with chronological age. Clarkson, Spirduso, and Clifford did not follow their participants to test the relationship between reaction time and survival.

Third, many of the oldest Goessel women were unable to participate in the neuromuscular, strength, and lung function tests. It is likely that those subsequently deceased participants who could complete these tests were highly fit and that the younger predicted age among these Goessel women reflected their select nature. The one subject, born in the 1880s, who participated in neuromuscular tests had a faster reaction time than the average for women 10 years her junior. Researchers have previously suggested that successively older groups of individuals are increasingly more select and thus less representative of their birth cohorts. Clement (1974) hypothesized that the select nature of older individuals may cause an underestimate of age differences with respect to physical performance tests. This cannot be tested cross-sectionally, however (Botwinick 1973). Using longitudinal data, it can be documented that poor performers drop out (Baltes et al. 1971; Jarvik and Falek 1963; Riegel et al. 1967). These researchers anticipated the concept now called frailty, which states this phenomenon in reverse: that the frailest members of a birth cohort die first (Vaupel et al. 1979). Regardless of the terminology, the Mennonite results support this circumstance. Forty-one percent of the Mennonite clinic participants who have subsequently died were less than 80 years old at the time of death. They would not have been included if the research had been conducted 10 years later. It can be argued legitimately that the 16% of participants who died by age 70 died prematurely. We plan to examine the differences between those who died prematurely and those who died at advanced ages in future research.

To summarize, our Midwest Mennonite research sample, consists of participants from two communities. These Mennonites provide a unique data set because (1) both women and men are included, (2) the participants do not smoke, and (3) the participants consume only small amounts of wine. This lifestyle eliminates two leading negative health influences. Available data include one set of variables collected in both communities plus additional variables collected in only one community. Women and

men are always analyzed separately, but for some analyses the communities are pooled. The analyses by sex, community, and variable set yield eight comparisons; the pooled samples yield two more. Based on their functional age residuals, individuals are divided into four groups based on functional age (younger, older) and survival status (alive, dead).

Computing functional-biological age based on stepwise multiple regression is not fully satisfactory for predicting 10-year survival, even when the independent variables are associated with mortality. Although the multiple regression method has been criticized by some researchers, it has not been previously tested against prediction of survival. The ranges of functional age residuals parallel increases in chronological age among research participants, demonstrating that the effect of chronology is not fully removed by the regression procedure. The variances associated with age-group residuals, however, are not significantly different. In some cases the relationships of independent variables with chronological age differ by sex. In general, these variables are related to body morphology or serum lipids and electrolytes. In the regression equations metabolic wastes and body morphology are more important for women than for men. Lipids and electrolytes are more important for men. The relative importance of specific variables differs by community and sex, however. When the equations are based on community-specific variables, strength and reaction time variables enter the equations for Goessel residents; self-rated health enters the equation for Henderson men.

In six of our ten comparisons, chi-square statistics indicate that functional status does successfully predict future survival ($p < 0.01$). For the same six comparisons, t tests indicate that the mean functional ages for the younger and older groups are significantly different ($p < 0.01$). Also, for the same six comparisons risk ratios indicate that those who are functionally older are at significantly greater risk of dying than their functionally younger counterparts. In three other comparisons the risk ratio results are consistent but not significant. In most cases, when community-specific variables are added to the regression model, the R^2 values increase, but this does not enhance the prediction of future survival.

In conclusion, this research is unique in its effort to test a measure of relative functional-biological age against future survival. Our results support the concern surrounding the use of chronological age as the dependent variable in the multiple regression method expressed by Costa and McCrae (1977). It is clear that the method cannot fully remove the effect of chronology. We agree that variables related to chronological age or function but not to mortality can complicate an understanding of the relationship of relative function and survival, as suggested by Brown and Forbes (1976) and Voitenko and Tokar (1983). This research supports the evidence provided by Baltes et al. (1971), Jarvik and Falek (1963), and Riegel et al. (1967) and suggestions expressed by Botwinick

(1973) and Clement (1974) that older participants are the select survivors from their birth cohorts. The 16% of Mennonite participants who died by age 70 sustains the hypothesis of Vaupel et al. (1979) that the frailest members of a birth cohort die first. In our opinion the observed sex differences in the relationships between independent variables and chronological age and in the relative importance of different variables, by sex, argue that women and men should not be pooled for analysis regardless of the significance of the sex differences. On the basis of differences in the relative importance of specific independent variables and the differential success in predicting survival by community, we strongly recommend that researchers use caution when trying to apply the results from one population to another. It seems logical to expect that a better understanding of aging will be found in the commonalities of results between communities and populations but that these can easily be masked by community-specific conditions.

Acknowledgments This research was supported in part by the National Institutes of Health under grant AG01646-01. We are grateful to the Goessel and Henderson Mennonites, without whose support and participation this study would not have been possible. We also want to thank the reviewers, who gave their time to make some excellent suggestions for organization and additions to this manuscript.

Received 17 August 1992; revision received 4 March 1993.

Literature Cited

Baltes, P.B., K.W. Schaie, and A.H. Nardi. 1971. Age and experimental mortality in a seven-year longitudinal study of cognitive behavior. *Dev. Psychol.* 5:18–26.

Bell, B. 1972. Significance of functional age for interdisciplinary and longitudinal research in aging. *Aging Hum. Dev.* 3:145–147.

Benjamin, H. 1947. Biologic versus chronologic age. *J. Gerontol.* 2:217–227.

Borkan, G.A. 1978. The assessment of biological age during adulthood. Ph.D. dissertation, University of Michigan, Ann Arbor.

Borkan, G.A., D.E. Hults, and P.J. Mayer. 1982. Physical anthropological approaches to aging. *Yrbk. Phys. Anthropol.* 25:181–202.

Botwinick, J. 1973. *Aging and Behavior*. New York: Springer.

Botwinick, J. 1981. *We Are Aging*. New York: Springer.

Botwinick, J. 1984. *Aging and Behavior*, 3d ed. New York: Springer.

Botwinick, J., R. West, and M. Storandt. 1978. Predicting death from behavioral test performance. *J. Gerontol.* 33:755–762.

Brown, K.S., and W.F. Forbes. 1976. Concerning the estimation of biological age. *Gerontology* 22:428–437.

Clarkson, P. 1978. The relationship of age and level of physical activity with the fractionated components of patellar reflex time. *J. Gerontol.* 33:650–656.

Clement, F. 1974. Longitudinal and cross-sectional assessments of age changes in physical strength as related to sex, social class, and mental ability. *J. Gerontol.* 29:423–429.

Costa, P.T., Jr., and R.R. McCrae. 1977. Functional age: A conceptual and empirical critique. Paper presented at the conference Epidemiology of Aging, Bethesda, MD, March 28–29, 1977.

Crawford, M.H., and L. Rogers. 1982. Population genetic models in the study of aging and longevity in a Mennonite community. *Soc. Sci. Med.* 16:149–153.

Devor, E.J., and M.H. Crawford. 1984. Family resemblance for normal pulmonary function. *Ann. Hum. Biol.* 11:439–448.

Devor, E.J., M.H. Crawford, and W. Osness. 1985. Neuromuscular performance in a Kansas Mennonite community: Age and sex effects in performance. *Hum. Biol.* 57:197–211.

Devor, E.J., M. McGue, M.H. Crawford et al. 1986. Transmissible and nontransmissible components of anthropometric variation in the Alexanderwohl Mennonites. I. Description and familial correlations. *Am. J. Phys. Anthropol.* 69:71–82.

Durbina, T.L., A.Y.A. Mints, and E.V. Zhuk. 1984. Biological age and its estimation. III. Introduction of a correction to the multiple regression model of biological age and assessment of biological age in cross-sectional and longitudinal studies. *Exp. Gerontol.* 19:133–143.

Facchini, F., P. Gueresi, and D. Pettener. 1992. Biological age in Italian adults: Influence of social and behavioral factors. *Ann. Hum. Biol.* 19:403–420.

Furukawa, T., M. Inoue, F. Kajiya et al. 1975. Assessment of biological age by multiple regression analysis. *J. Gerontol.* 4:422–434.

Handler, P., ed. 1970. *Biology and the Future of Man.* New York: Oxford University Press.

Idler, E.L., and R.J. Angel. 1990. Self-rated health and mortality in the NHANES-1 epidemiologic follow-up study. *Am. J. Public Health* 80:446–452.

Jarvik, L.F., and A. Falek. 1963. Intellectual stability and survival in the aged. *J. Gerontol.* 18:173–176.

Kaplan, G., V. Barell, and A. Lusky. 1988. Subjective state of health and survival in elderly adults. *J. Gerontol.* 43:S114–S120.

Kohn, R.R. 1971. *Principles of Mammalian Aging.* Englewood Cliffs, NJ: Prentice Hall.

Larue, A., L. Bank, L. Jarvik et al. 1979. Health in old age: How do physicians' ratings and self-ratings compare? *J. Gerontol.* 34:687–691.

Mausner, J.S., and S. Kramer. 1985. *Epidemiology: An Introductory Text.* Philadelphia, PA: W.B. Saunders.

Palmore, E.B. 1982. Predictors of the longevity difference: A 25-year follow-up. *Gerontologist* 22:513–518.

Riegel, K.F., R.M. Riegel, and G. Meyer. 1967. A study of the dropout rates in longitudinal research on aging and the prediction of death. *J. Personality Soc. Psychol.* 5:342–348.

Ries, W., and D. Pothig. 1984. Chronological and biological age. *Exp. Gerontol.* 19:211–216.

Sokal, R.R., and J. Rohlf. 1981. *Biometry*, 2d ed. San Francisco, CA: W.H. Freeman.

Spirduso, W. 1975. Reaction time and movement time as a function of age and physical activity level. *J. Gerontol.* 30:435–440.

Spirduso, W., and P. Clifford. 1978. Replication of age and physical activity effects on reaction and movement time. *J. Gerontol.* 33:26–30.

Steuer, J., A. Larue, J.E. Blum et al. 1981. "Critical loss" in the eighth and ninth decades. *J. Gerontol.* 36:211–213.

Strehler, B.L. 1977. *Time, Cells, and Aging*. New York: Academic Press.
Uttley, M. 1991. The relationship of measures of biological age to survivorship among Mennonites. Ph.D. dissertation, University of Kansas, Lawrence. Ann Arbor, MI: University Microfilms.
Vaupel, J.W., K.G. Manton, and E. Stallard. 1979. The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography* 16:439–454.
Voitenko, V.P., and A.V. Tokar. 1983. The assessment of biological age and sex differences of human aging. *Exp. Aging Res.* 9:239–244.
Waring, J. 1978. *The Middle Years: A Multidisciplinary View*. New York: Academy for Educational Development.
Webster, I.W., and A.R. Logie. 1976. A relationship between age and health status in female subjects. *J. Gerontol.* 31:546–550.