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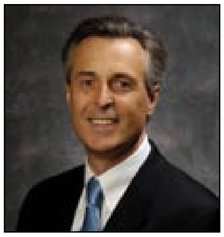
Re•FLECTIONS

RGA's Medical Underwriting Newsletter

LETTER FROM THE EDITOR



Dear Readers:

This edition of *Re•FLECTIONS* contains two articles that pertain to mortality assessment of the elderly. Due to demographic shifts and a need for financial planning in the elderly population, we will likely continue to see large numbers of older insurance applicants, and we need to refine our skills in assessing mortality risk in this group. Part of this assessment concerns evaluating the "vitality" or conversely the "frailty" of the elderly applicant. In this edition, I discuss how cognitive function and physical function for the elderly can be assessed for this purpose.

I hope you enjoy this issue of *Re•FLECTIONS* and that the content stimulates your interest for subsequent editions.

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THE VALUE OF SCREENING FOR COGNITIVE FUNCTION IN THE ELDERLY

By J. Carl Holowaty, M.D.

Underwriting of the elderly involves assessment of factors that differ from those that are traditionally of concern in the non-elderly. While it is usually safe to assume that most adults are able to lead physically and socially active lives and have the mental faculties to handle everyday tasks, this is not always the case in the elderly, defined in this article as those greater than 70 years old. This article examines the risk associated with declining cognitive function in the elderly, the ways of measuring cognitive function and how it relates to mortality expectations.

The term "cognition" refers to mental activities such as thinking, attention, reasoning, decision-making, and dealing with concepts. The process of bringing together and coordinating information for a purpose, such as decision-making, is called "executive functioning." These are all activities that are used in daily life to aid in the Instrumental Activities of Daily Living (IADLs) such as shopping, banking, travel planning, and meal preparation. Unfortunately, for reasons not yet fully understood, these functions are subject to decline over time and can eventually contribute to overall frailty in the elderly and are often associated with similar declines in physical activity and socialization. These additional subjects will be discussed in greater depth in subsequent articles in this publication.

The development of cognitive deficit is usually manifested by memory impairment and at least some evidence of aphasia, apraxia, agnosia, and a disturbance of executive functioning.

Aphasia – a disorder of speaking in which the person has great difficulty articulating words.

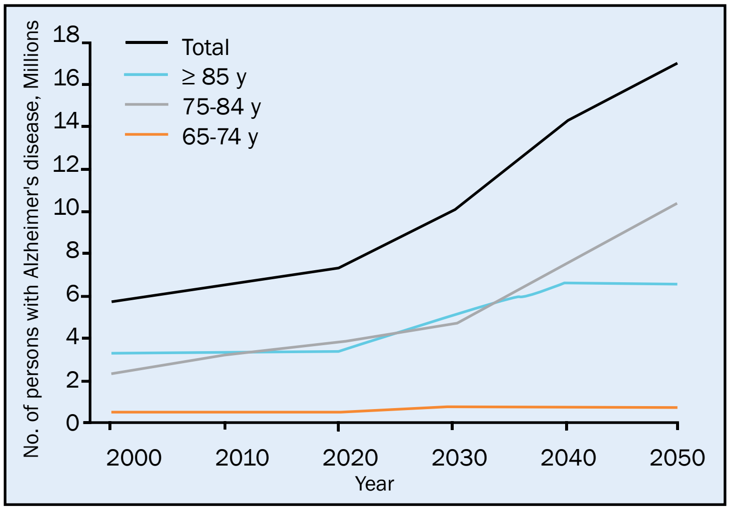
Apraxia – a disorder of movement caused by damage to the brain.

Agnosia – a disorder in which the affected person is unable to make meaning out of one or more of their senses (sight, hearing, touch, taste, or smell).

Loss of cognitive function, when severe enough, is called *dementia*. Dementia can be caused by a variety of conditions. The most common cause, Alzheimer's disease (AD) accounts for about 60% of the total. Vascular dementia, also known as multi-infarct dementia, accounts for about 30%. The remaining 10% is caused by other conditions such as trauma, Pick's disease, Parkinsonism, HIV, Lewy body dementia, Huntington's disease, and other fairly rare conditions.

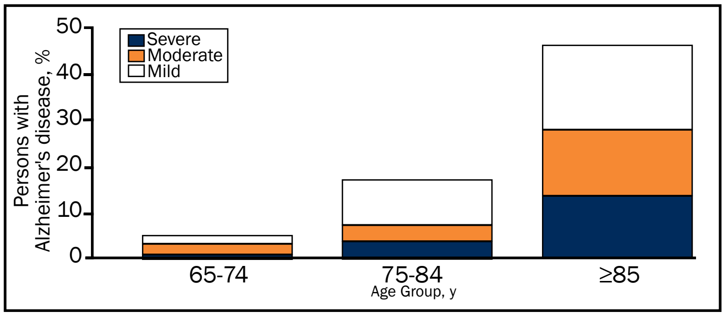
Testing for dementia may include a detailed medical history of a person and his or her family, physical examination, psychological assessment, specific cognitive testing, neurological examination, lab tests, and brain scans. In some cases, definitive diagnosis may include autopsy derived histopathological examination for confirmation.

In order to gauge the scope of cognitive disorders in the elderly, it is probably easiest to evaluate the evidence relating to Alzheimer's disease, since it is the best-studied of the major causes of dementia. Unfortunately, even in this well-studied condition, prevalence rate estimates may be inaccurate since there is a continuum between normal cognition and recognizable cognitive impairment. Screening tests that detect very early cognitive changes will produce higher prevalence rates than those that detect more advanced disease. With this in mind, it is clear from clinical studies that AD is more common in the elderly than in younger adults. Furthermore, general population studies suggest that changing U.S. demographics related to mortality improvements and the aging of the "Baby Boomers" will affect the prevalence of AD in the future.



Projected number of persons in U.S. population with Alzheimer's disease by age groups, 65 to 74 years old, 75 to 84 years old, and 85 years and older, using the 2000 U.S. Census Bureau middle series estimate of population growth.[1]

Another representation of the prevalence of AD is expressed in the table below, which relates Mini-Mental State Examination (MMSE) scores to various age groups in the elderly population. This test is one of the clinical standards for cognitive testing and is reasonably reliable for detecting moderate and severe disease. It does have some limitations in detecting early cognitive changes. It is reasonable to assume that the mildest forms of AD may not be detected and as such the portion of the bar graphs related to mild AD are probably smaller than would be the case if more sensitive testing were used.



Even with the limitations in test sensitivity, it is clear that in the oldest of the tested age groups AD is extremely common. It is therefore critical to delineate the expected mortality concerns associated with the different degrees of severity of AD. The next graph illustrates the survival after initial diagnosis, by gender and different age bands.

Comparison of Life Expectancy by Quartiles of Study Participants and U.S. Population[2]

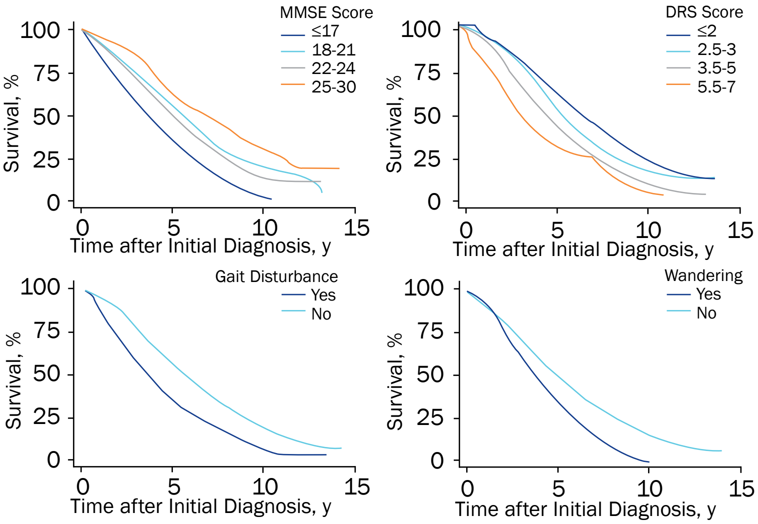
Larson et al. "Survival after Initial Diagnosis of Alzheimer Disease"
6 April 2004/Annals of Internal Medicine/Vol. 140

	Life Expectancy Quartiles														
	Age 70 y			Age 75 y			Age 80 y			Age 85 y			Age 90 y		
	75%	50%	25%	75%	50%	25%	75%	50%	25%	75%	50%	25%	75%	50%	25%
	y														
Women															
U.S. Population	21.3	15.7	9.5	17	11.9	6.8	13	8.6	4.6	9.6	5.9	2.9	6.8	3.9	1.8
Patients with Alzheimer's disease (*n* = 341)	12.3	8.0	5.9	10.0	5.8	4.0	8.7	5.3	3.2	6.7	3.9	2.4	5.2	2.1	1.6
Men															
U.S. Population	18	12.4	6.7	14.2	9.3	4.9	10.8	6.7	3.3	7.9	4.7	2.2	5.8	3.2	1.5
Patients with Alzheimer's disease (*n* = 180)	5.1	4.4	3.1	7.2	4.5	2.3	6.8	3.6	2.2	5.0	3.3	2.3	4.9	2.7	0.9

The diagnosis of AD clearly confers a distinct survival disadvantage for both males and females at all the tested ages. It is not clear in this study, however, what the survival is by severity of AD, and what the distribution of severity was in the study. For instance, if the patient distribution were heavily weighted toward moderate and severe disease rather than mild or minimal disease, survival could appear worse than if the situation were reversed. Further studies, however, shed some light on this concern. The following graphs relate survival to a person's MMSE score as well as the subject's Dementia Rating Score (DRS), with lower scores reflecting more advanced cognitive impairment. It is apparent that lower scores (more advanced disease) are associated with poorer survival. The graphs also illustrate the importance of gait disturbance and "wandering" as survival predictors.

Prevalence of severe (Mini-Mental State Examination score ≤9), moderate (Mini-Mental State Examination score, 10-17), and mild (Mini-Mental State Examination score, ≥18) Alzheimer's disease, in each of three age groups, in the community population providing data for these estimates.[1]

Kaplan-Meier Survival Estimates[2]



The information presented so far in this article shows that AD is increasingly common as age increases within the elderly population and is associated with significant excess mortality that is related to the severity of the condition. Although testing for cognitive impairment in younger populations may not provide much mortality benefit compared to the cost of routine testing, this benefit would increase at the older ages.

Testing for cognitive impairments can be done in a variety of ways. The remainder of this article outlines some of the test procedures and discusses some of their attributes and shortcomings. First, however, a better understanding of the presentation of AD would be useful.

AD Presentation

AD usually manifests itself in several ways. It typically involves memory loss, especially of recent events. There is also often a loss of language skills, including an inability to remember a noun or name, repeating of words, or sometimes "nonsense" speech. There may also be an inability to recognize familiar people or objects. The loss of spatial skills may affect everyday tasks such as dressing and sitting down, resulting in possible falls. More subtly, AD may present as the loss of initiative, forgoing the pleasurable activities that were previously important or a regular lifestyle feature. While all of these signs and symptoms could indeed represent dementing illness, they may also be due to affective disorders such as depression, another common condition in the elderly.

Ideally, a test for cognitive functioning should measure all of these functions. For insurance purposes it should be easy to administer and interpret and be accurate enough to ensure a minimum of both false negatives and false positives. It should also be socially acceptable and culturally sensitive.

Reisberg et al, have delineated seven stages of AD:[3]

Stage 1: No impairment

Stage 2: Very mild decline

Stage 3: Mild decline

Stage 4: Moderate decline (mild or early stage)

Stage 5: Moderately severe decline (moderate or mid-stage)

Stage 6: Severe decline (moderately severe or mid-stage)

Stage 7: Very severe decline (severe or late stage)

While it is relatively easy for even basic cognitive testing to detect the latter stages of AD, this becomes much more difficult for the earlier stages. This is not entirely due to the tests themselves. As a clinician, it is usually apparent that people in the early- and mid-stages of AD can have "good days." On those particular days, they function normally and some would probably pass the cognitive screening tests. Conversely, a normal person, through lack of attention or motivation, might be ranked as having possible AD. In a clinical setting, re-testing would sort out this matter, but for the insurer, we usually only have one chance to make our decision.

Part of the value of cognitive screening tests is in their "sensitivity and specificity" and their positive and negative predictive value, which are defined below:

Sensitivity	The probability that a screening test is positive when the person has the disease. Sensitivity = True Positives/(True Positives + False Negatives)
Specificity	The probability that a symptom is not present (or screening test is negative) given that the person does not have the disease. This is also known as true negative rate. Specificity = True Negatives/(False Positives + True Negatives)
Positive Predictive Value	The probability that a person has the disease if the test result is positive. PPV = True Positives/(True Positives + False Positives)
Negative Predictive Value	The probability that a person does not have the disease if the test result is negative. NPV = True Negatives/(False Negatives + True Negatives)

There are a variety of tests for cognitive function that are currently being used. It is not possible to discuss all of different tests, but some of the most common are:

- AD8 – Alzheimer's disease 8
- AQT – Alzheimer's Quick Test
- CDT – Clock Drawing Test
- CA – Correspondence Analysis Weighted DWR
- DWR – Delayed Word Recall
- EMST– Enhanced Mental Skills Test
- MMSE – Mini-Mental State Examination
- MCAS – Minnesota Cognitive Acuity Screen
- SPMSQ – Short Portable Mental Status Questionnaire

Although all of these tests are used to aid in the diagnosis of AD, all do not consider the same factors. For example, the AD8 asks an informant rather than the patient for changes in various aspects of cognition. The AQT test considers processing speed rather than content. The CDT test primarily evaluates spatial perception skills. Delayed word recall tests evaluate working memory. The EMST is a relatively comprehensive test, measuring many of the aspects of cognitive function. The MCAS includes calculation in its measurements.

A much more thorough explanation of the tests (as well as a detailed evaluation of mortality related to cognitive disorders) is available online at www.rgare.com/underwritingconnection in a webinar-based PowerPoint presentation titled "Cognitive Testing." I encourage you to visit this Web site.

A review of available clinical literature suggests the following comparative factors for the above tests, as shown in the table below:

TEST	COST	TIME	RELIABILITY	SENSITIVITY	SPECIFICITY
AD8	Inexpensive	3-5 minutes			
AQT	$2.00 - $3.00	3-5 minutes		95-99.9%	97-99%
CDT				87%	82%
CA	High	15 minutes	MCI vs. Normal MCI/mild dementia vs. Normal Mild dementia vs. Normal	95% 97% 96%	88% 88% 99%
DWR	High	15 minutes		89-96%	98-100%
EMST		<15 minutes	Overall MCI Mild dementia Mild dementia	97% 94% 98% 100%	?
MMSE	Moderate	5-10 minutes	For mild disease Overall	Low 87%	59-96% Average-82%
MCAS				97.5%	98.5%
SPMSQ	Moderate	10 minutes		55-92%	72.2-96%)

This suggests that all of these tests have both value and limitations in their ability to meet the criteria for an ideal insurance screen for AD and other causes of dementia.

Summary

In summary, excess mortality is related to cognitive decline. This state increases with age and the rates are very high above the age of 80. Survival is related to the severity of the condition at the time of presentation. While all of the commonly used cognitive screens are effective at detecting moderate and severe dementia, they are less reliable in evaluating the milder forms of dementia.

When evaluating the impact of the use of cognitive screens in an insurance population, we must consider several factors that may not be as critical in the general population. It is apparent that the worst survival is likely to occur in people with severe disease. Fortunately, it is not likely that people with severe dementia will actually be life insurance candidates, unless their condition is grossly misrepresented by various parties. We do have a fair degree of certainty that almost any of the screens will be reasonably effective at detecting the moderate stages of dementia (unless that person is having a particularly "good day"). While this is reassuring, it is also likely that at least some of these same people have already been identified as having AD from other routine application sources such as attending physician statements, so the cognitive screen is merely confirming what we would otherwise already know.

The most value may be derived from detecting applicants with relatively mild cognitive impairment. Unfortunately, this is the group for which the accuracy of the testing is most questionable. As implied above, there is a risk in this group of significant numbers of false positives and false negatives that may not be completely acceptable in a business setting. While there is no doubt value in correctly assigning mortality expectations to those with cognitive impairment, it is important to not overestimate the value of screening in the insured population, such as might happen if only general population statistics are considered. Ultimately, insured population studies using one's own experience will be the best guide to evaluating the usefulness of screening procedures.

Several considerations need to be made:

1. To screen or not to screen?
2. At what age and amount to screen?
3. Which specific screen to use?
4. How to adjudicate the results of the screen?
5. Legal? (Can and should a contract be made in good faith when the applicant's tests suggest early dementing illness). This may be important if the issue of misrepresentation arises.

Once again, please visit:
www.rgare.com/underwritingconnection
for more detail on this article.

References

[1] Hebert, L., Scherr, P., Bienias, J., Bennett, D., Evans, D. *Alzheimer Disease in the US Population*. Reprinted, Arch Neurol / Vol. 60, Aug. 2003.

[2] Larson, E., Shadlen, M., Wang, L., McCormick, W., Bowen, J., Teri, L., Kukull, W., *Survival after Initial Diagnosis of Alzheimer Disease*. Annals of Internal Medicine, Vol. 140, Number 7, April 6, 2004.

[3] Reisberg, B., Ferris, S.H., de Leon, M.J., et al, *The global deterioration scale for assessment of primary degenerative dementia*. American Journal of Psychiatry, 1982, 139: 1136-1139. Copyright ©1983 by Barry Reisberg. Reproduced with permission.

THE VALUE OF SCREENING FOR PHYSICAL FUNCTION IN THE ELDERLY

By J. Carl Holowaty, M.D.

The ability to exercise is one measure of vitality among the elderly. Examination of the clinical linkage between exercise capacity and mortality in the general elderly population can be helpful in estimating the benefits of screening elderly insurance applicants with the intent of improving risk stratification in this segment of the population. The implication of this type of selected screening is that mortality gains may be expected. Clearly, the extent of the gains has to be understood in order to have a realistic expectation of overall mortality experience.

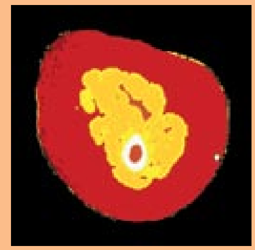
This article examines the link between physical function and mortality in the elderly, and illustrates some of the mechanisms for the adverse mortality associated with a lack of vitality.

Part of the aging process involves a gradual loss of muscle mass with resultant losses in strength/function. This occurs even in the active elderly. This phenomenon is called sarcopenia.

The effect of aging on muscle mass, strength and exercise capacity[1]

- *Sarcopenia* - (def) The loss of muscle mass/function in normal aging

CT Scan of a thigh muscle of a healthy young adult. The thigh bone is white. The muscle area (yellow) is not indicative of sarcopenia.



CT Scan of a thigh muscle of a sedentary older adult. The thigh bone is white. The greatly reduced muscle area (yellow) indicates sarcopenia.

Sarcopenia has significant implications, since even a 5% loss of muscle mass leads to decreases in strength and independence. Generally, losses of greater than 40% of muscle mass are fatal. Sarcopenia usually begins at about age 45 with approximately 1% muscle mass lost per year. This loss contributes to frailty in the elderly and may be accelerated by a protein-deficient diet (common in the elderly) and a sedentary lifestyle. It may also be exacerbated by chronic illness or injury. In the next edition of *Re•FLECTIONS*, I will attempt to link cognitive function, physical function, and socialization to illustrate the interplay between these elements of vitality and demonstrate how social isolation can contribute to sarcopenia, frailty, and ultimately mortality.

The next segment of this article delineates some of the linkages between mortality and the various aspects of physical fitness. The primary components of physical fitness are:

1. Body composition (muscle mass/tone)
2. Cardio-respiratory endurance
3. Muscle strength
4. Muscular endurance
5. Flexibility
6. Agility/balance/body awareness

The relative ratio of body components in a middle-aged adult male are:

Body Components of Standard Man

- *Muscle Mass* *29%*
- *Fat Mass* *26%*
- *Bone* *7%*
- *Connective Tissue* *7%*
- *Visceral Mass* *6%*
- *Immune Cell Mass* *4%*
- *Extra-cellular Water* *22%*

In females, the percentage of body fat is higher, and that of muscle mass is lower. During the aging process, as stated earlier, the amount of muscle mass diminishes, often replaced by fat mass.

While it may be intuitive to suspect that increasing adiposity is associated with decreasing fitness, this may not be the case in the elderly.

The results of a study that examined this relationship in the elderly are summarized below:

Body Adiposity and Fitness
(Mean age of subjects is 70)
J. Am. Geriatric Soc. 1991 Dec; 39(12): 1189-93
Reed, R.L. Yokum, K, Pearlmutter, L, Meredith, K.E., Mooradian, A.D.

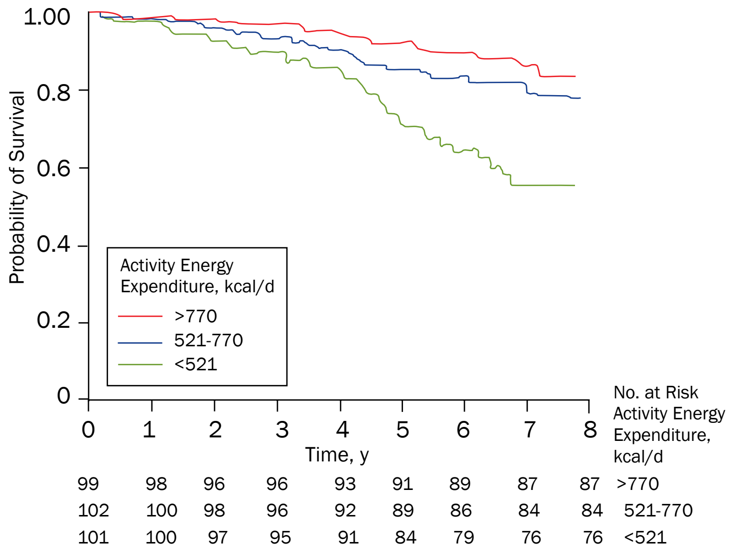
	Females	Males
Lowest tertile of activity	38.0%	27.9%
Middle tertile of activity	36.0%	28.1%
Highest tertile of activity	37.0%	28.5%

This study suggests that using a person's percentage of body fat may not be a reasonable surrogate for physical fitness. This may also at least partially support the weaker relationship between obesity and mortality in the elderly as compared to younger adults.

Physical fitness in the elderly and its relationship to mortality has been well-studied, even if not so well as the same relationship in younger adults. One of the studies *(302 community-dwelling participants age 70-82, followed for six years, using double-labeled water technique)*[3] indicates that any level of physical activity in the elderly can lower mortality risk. Higher levels of physical activity are associated with reduction in coronary heart disease, cancer incidence, falls, and physical disability.

Activity Energy Expenditure[4]

Adjusted for Age and Sex



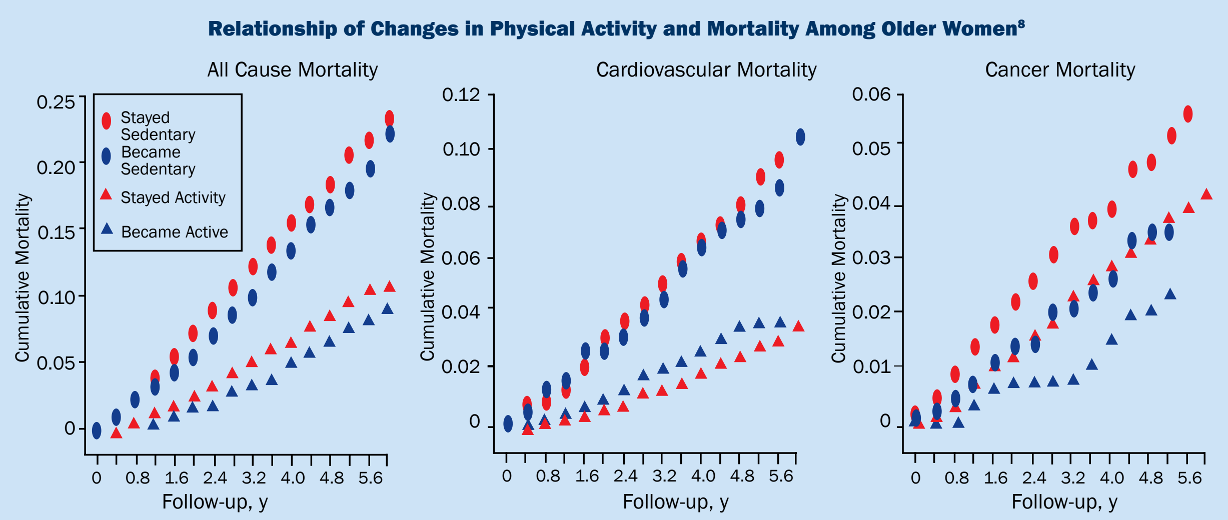
A further study *(2,113 participants from general Taiwan population > 65 years old studied for two years)*[5] examined the linkage between mortality and exercise intensity, frequency, and duration. It concluded that regular exercisers (in the general population) had a 35% reduction in risk of death compared to sedentary individuals. Of the three exercise components, only intensity was significantly associated with mortality reduction. Other studies have evaluated the mortality associated with the ability to do a timed walk down a ¼-mile corridor *(3,075 community-dwelling, well participants age 70-79; study duration five years)*[6]. Inability to complete the course was associated with a higher risk of overall mortality and cardiovascular disease. Among those able to complete the course, each additional minute of performance time was associated with a 29% higher rate of mortality. This test was believed to be a useful substitute for the treadmill test as a predictor of adverse outcome in the elderly.

An interesting study done on participants in the Nurses Health Study *(18,766 participants in Nurses Health Study age 70-81; study duration eight years)*[7] showed that less cognitive decline was noted in women who were more active. This is important to consider when trying to correlate the expected mortality gains linked to cognition, physical and social function. There may be a certain degree of association among all these measures of vitality and it is reasonable to assume that the mortality gains will not necessarily accrue in a purely cumulative fashion.

One of the studies examined the effect of changes in women's physical function. They measured the mortality of women who, during the study:

1. Maintained their exercise level
2. Started exercising
3. Stopped exercising
4. Remained sedentary

The results are illustrated in the table to the right:



The results certainly suggest that there is considerable mortality benefit associated with exercise, even if one has been sedentary up until that point.

Additional studies and their results are described at greater length on a recorded webinar entitled,"Older Age Underwriting: The Value of Functional Assessment" at RGA's Web site www.rgare.com/underwritingconnection. These studies demonstrate that increasing levels of exercise tolerance in the elderly provide mortality benefits for men and women, both to those who are well and to those with a history or CAD. They also show that increasing levels of exercise tolerance provides some benefits regarding cognitive function, risk of hip fracture, and possibly falls.

Exercise Tolerance, Fitness Measures For The Elderly

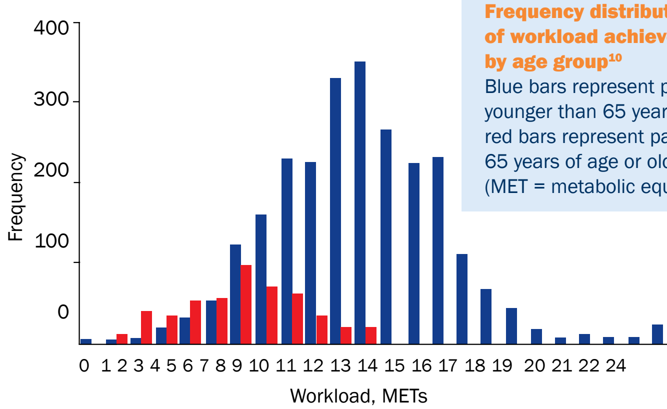
There are a variety of ways to measure exercise tolerance or fitness in the elderly. They will be summarized in two tables at the end of this section of the article and are described more thoroughly in the previously mentioned Web site. The simplest means is to do a questionnaire-based self-reported activity check. This is relatively inexpensive, but subject to recall bias and possibly anti-selection. In addition, there may be a tendency among applicants to portray themselves in a more favorable light than is deserved in terms of exercise frequency and intensity.

Another fairly simple test to administer is the Timed Up and Go (TUG) test. This test measures the time it takes a person to stand up from an armchair, walk 10 feet, turn, walk back to the chair, and sit down. In addition to measuring the speed of this complex activity, it is a reasonable gauge of cognition and balance. Generally test times of less than 12 seconds are favorable, with this time representing the 90th percentile for the well elderly.

The Six-Minute Walk Test (6MWT) measures the maximum distance that a person can walk in six minutes. It is a sub-maximal test of aerobic capacity and a better measure of exercise endurance than maximal exercise capacity.

The Comfortable Gait Speed (CGS) and Fast Gait Speed (FGS) test measures gait speed over a relatively short distance and does not include endurance as a factor.

Treadmill testing is an effective way of assessing fitness is the elderly. After adjustment for clinical variables, workload (measured in metabolic equivalents or METs) was the only additional treadmill variable that was predictive for death *(514 community participants > 65 years of age, followed for six years)* [9]. Each MET increase in exercise capacity was associated with an 18% reduction in cardiac events among the elderly. Physical activity was inversely associated with coronary disease and all-cause mortality. The risk for coronary disease associated with inactivity was estimated to be of the same magnitude as that associated with hypertension, hypercholesterolemia, and smoking. The table below illustrates the distribution of workload in the general population, in both the elderly and younger adults. It is obvious that the elderly generally have a far-reduced work capacity compared to their younger counterparts.



Frequency distribution of workload achieved by age group[10]
Blue bars represent patients younger than 65 years of age; red bars represent patients 65 years of age or older. (MET = metabolic equivalent).

While the previous tests measure endurance and speed of activity, the Berg Balance Scale (BBS) is a comprehensive test of balance, one of the components of physical fitness. Its primary value is in determining the risk of falls.

The following two charts compare many of the tests that are commonly used in clinical medicine to evaluate fitness. The ratings represent my opinions of the relative merits and disadvantages of each of the tests.

Comparison of Tests - Measuring Physical Function

	Intensity	Duration	Frequency	Strength	Balance
Self-reported activity	?++	?++	?++	?++	?++
Corridor Walking	+++	+	n/a	+	++
TUG	++	n/a	n/a	++	++
6MWT	+++	+	n/a	+	++
BBS	n/a	n/a	n/a	++	+++
CGS-FGS	+++	n/a	n/a	++	++
TM	++++	+++	n/a	++	+++

Comparison of Tests

	Cost	Reliability	Time	Convenience	Safety
Self-reported activity	Low	+	+++	++++	++++
Corridor Walking	Moderate	+++	++	++	+++
TUG	Moderate	+++	++++	++++	+++
6MWT	Moderate	+++	++	++	+++
BBS	Moderate	+++	++	++	++
CGS-FGS	Moderate	+++	++	++	+++
TM	High	++++	+	+	++

This list is not intended to be comprehensive. For instance, it does not include a simple test such as the handgrip test for measuring strength. These tables show that each test measures some, but not all, of the components of fitness. Each test also has its own peculiar drawbacks, whether they are speed and cost of administration, accuracy, repeatability, convenience, or safety. They all provide effective ways to evaluate at least some of the elements of fitness, and when used in the insurance setting can assist in stratifying life and health risk.

Summary

Physical fitness in the elderly is clearly an important predictor for mortality. Although clinical studies suggest certain degrees of mortality improvement, it is important to recognize that the insured population may not have the identical degree of mortality improvement for a variety of reasons. For example, clinical studies probably do not have to deal with as much possible anti-selection risk inherent in a self-reported fitness questionnaire.

Another important consideration is the fact that physical fitness is a modifiable risk factor. While it is encouraging to know that one's mortality risk can be improved at any age merely by becoming more physically fit, it is also quite possible to worsen one's risk merely by decreasing or stopping one's activity levels. In younger adults, it is reasonable to assume that a middle-age person with a long history of physical fitness will likely continue to maintain these levels for many years to come. In the elderly, however, one's activities can be curtailed quite abruptly, either by volition or through even minor injuries or changes in health and social circumstance – such as the loss of a marital partner or associates. If this should happen, the expected mortality gains would rapidly regress.

Ultimately, the overall mortality gain to be expected in the physically fit elderly applicant needs to be evaluated in context with that same person's cognitive condition and social function, since these are all elements of "vitality." I will discuss some of these inter-relationships in the next edition of *Re•FLECTIONS*.

References

[1] Bliss, R., Low Protein + Low Exercise = Sarcopenia. Agricultural Research Magazine, Vol. 53, Number 5, May 2005.

[2] Reed, R.L., Yokum, K., Pearlmutter, L., Meredith, K.E., Mooradian, A.D. Journal of the American Geriatrics Society, 1991, 39(12): 1189-93.

[3] Manini, T., Everhart, J., Kushang, V., Schoeller, D., Colbert, L., Visser, M., Tylavsky, F., Bauer, D., Goodpaster, B., Harris, T., 302 community dwelling participants age 70-82, followed for six years, using double-labeled water technique, JAMA, 2006, 296: 171-179.

[4] Manini, T., Everhart, J., Kushang, V., Schoeller, D., Colbert, L., Visser, M., Tylavsky, F., Bauer, D., Goodpaster, B., Harris, T., Activity Energy Expenditure, JAMA, 2006, 296: 175.

[5] Tan, T.Y., Chang, H.Y., Tai T.Y., 2,113 participants from general Taiwan population > 65 years old studied for two years, American Journal of Preventive Medicine, 2006, 43(1): 36-41.

[6] Newman A. et al. 3,075 community dwelling well participants age 70-79, study duration five years, JAMA, 2006, 295: 2018-2026.

[7] Weuve, J., Kang J.H., Manson, J., Breteler, M., Ware, J., Grodstein, F., Nurses' Health Study, including 18,766 U.S. women age 70-81. JAMA, 2004, 292: 1454-1461.

[8] Gregg, E., Cauley, J., Stone, K., Thompson, T., Bauer, D., Cummings, S., Ensrud, K. (for the Study of Osteoporotic Fractures Research Group), Relationship of Changes in Physical Activity and Mortality Among Older Women, JAMA, 2003, 289: 2379-2386.

[9] Goraya, T. et al., 514 community participants > 65 years of age, followed for six years, Annals of Internal Medicine, June 2000; 132(11): 862-870.

[10] Goraya, T. et al. Prognostic Value of Treadmill Exercise Testing in Elderly Persons, Annals of Internal Medicine, June 2000; 132(11): 862-870.