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## The oldest old and the 90+ Study

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### Abstract

Memories are the gifts from friends and family that stay with us forever, unless a person develops Alzheimer's disease. Leon J. Thal left many, many memories, along with his desire to create a world where people did not lose them to the ravages of dementing illnesses. Working from the bench to the clinic, he was an incomparable leader, scientist, and educator to whom many, including myself, owe much. The present description of a clinical, genetic, and pathologic study of the oldest old contains much of Leon's influence. With data from >950 subjects, a brain repository, and our collection of DNA, the investigators of the 90+ Study are receptive to collaborations. Through our collective efforts, we will continue the scientific work that Leon so strongly supported.

### Keywords

Oldest old; Dementia; Alzheimer's disease

## 1. Introduction

The extreme elderly are the fastest-growing segment of our population. Currently numbering around 2 million, by 2050, about 10 million Americans will be aged 90 years [1]. Those aged >90 years will comprise almost 6% of the population in Japan, 4% in Italy, and 2.5% in the United States. The striking increase in the number of the oldest-old worldwide presents a public health challenge to promote the quality as well as quantity of life. Up to 50% of people in this age group will have dementia [2], and a greater percentage will endure functional disabilities and frailty (Fig. 1).

Initiated in 2003, the goal of the 90+ Study (based in Laguna Woods, CA) is to perform prospective clinical, pathologic, and genetic investigations in people aged 90 years. With a committed cohort of elderly research participants, we have assembled possibly the largest prospective study of oldest-old subjects in the world (n = 945), and we anticipate enrolling approximately 600 additional subjects. The survivors of the Leisure World Cohort Study, begun in 1981 (average age at enrollment, 73 years), comprise the population-based sample for our studies in the oldest-old.

## 2. The public health impact of dementia in the oldest-old

Only a handful of publications have reported age-specific and sex-specific incidence rates for dementia at ages >90. Although several investigations suggested a decline or leveling of dementia incidence in the oldest-old [3,4] particularly for men [3–6], our study indicates a

doubling of the incidence with every 5 years of age for both men and women, similar to findings for younger ages [7]. We believe that ours is the first investigation to demonstrate this consistent doubling in both sexes, similar to subjects between ages 65 and 85 years. For the rapidly growing number of people in their 90s and beyond, the risk of developing dementia appears extraordinarily high. By the middle of the century, we will have as many people with dementia in this age group as we currently have in the United States at all ages.

### 3. Risk factors and protective factors for dementia

Dementia risk factors and protective factors identified in younger subjects may not be relevant for the oldest-old. For example, whereas physical activity and estrogen therapy were associated with a decreased risk of dementia in the younger elderly [8–11], our preliminary investigations, with data from the 1980s, associate these factors with increased longevity [12,13], but not dementia, in people age 90 and older. Studies of risk factors in the oldest-old are scarce, but such data are necessary to identify potential factors that may lead to cost-effective interventions relevant to the health of the rapidly growing number of nonagenarians and centenarians.

### 4. Motor and physical performance

In 90+-year-olds, motor abilities (such as speed, power, and dexterity) and physical performance measures (such as timed walking and hand grip) decline with age and show a wide spectrum of abilities. Increasingly, it appears that these motor and physical declines may be associated with declines in cognition [14], and an increased risk of dementia, disability, and death. One recent study showed that the 3-year risk of dementia was increased in individuals with poor physical performance as measured by walking time, chair-stands time, standing balance, and hand grip (mean age, 73 years) [15]. Our cross-sectional preliminary study found a similar relationship in our 90+-year-old subjects (Fig. 2). The association between motor, physical-performance, and cognitive/functional declines in advanced age may reflect common pathways that may involve neurodegenerative, vascular, or other age-associated mechanisms.

### 5. Pathologic changes in the brains of the oldest-old

Several investigations, including our own [16], noted that the oldest-old participants who die with dementia frequently do not have the high amounts of amyloid or neurofibrillary pathology generally associated with dementia [17,18]. On the other end of the spectrum, studies found that very elderly subjects who die without overt signs of dementia frequently have significant AD pathology [17,19–21]. We have seen a handful of these cases, including a nondemented 97-year-old woman with an apolipoprotein E 2/2 genotype [22]. In our preliminary studies, we found no relationship between amyloid staging and cognition, and a weak relationship between tangle staging and cognitive status. However, brain weights in our study [16] and in others [19] appear relevant to the preservation of cognition. Of all measures studied to date, presynaptic proteins correlate most strongly with cognitive function and a diagnosis of dementia in the oldest-old [23]. Unlike amyloid and other pathologic measures, the synaptophysin protein was significantly reduced in demented subjects, and correlated with the Mini-Mental State Examination and other neuropsychological test scores, particularly those sensitive to executive function (Fig. 3).

### 6. Results from the 90+ Study: factors associated with longevity

In the 13,978 members of the Leisure World Cohort, longevity was associated with:

- Postmenopausal estrogen therapy: The risk of death decreased with both increasing duration and decreasing years since last use [12].
- Body mass index: At study enrollment (average age, 73), body mass index (BMI) showed a reverse J-shaped relationship with mortality. Both being under-weight and obese increased the risk of mortality. Being overweight or obese at age 21 also increased mortality [24].
- Alcohol: Those who drank 2 drinks/day had a 15% reduced risk of death; the decreased risk was not limited to one type of alcohol [25].
- Caffeine: Caffeine intake exhibited a U-shaped mortality curve [26].
- Physical activities: Mortality was incrementally reduced with amount of time spent in physical activities up to 45 minutes/day (a 10% to 25% reduction), after which a constant benefit was observed (a 21% to 25% reduction) [13].
- Nonphysical activities: Mortality was reduced with 1 hours/day spent in these activities, and the magnitude of the reduction increased with additional time spent in nonphysical activities.
- Intake of antioxidant vitamins (A, C, or E) was not associated with longevity [27].

## 7. Results from the 90+ Study: risk factors for prevalent dementia

We explored the associations between prevalent dementia and the above variables, collected as part of the baseline survey for the Leisure World Cohort Study (1981 to 1985). After adjusting for age and sex, prevalent dementia in 90+-year-olds was not related to estrogen therapy, BMI, intake of supplemental vitamins A, C, and E, total intake of vitamin A, consumption of alcohol or caffeine, or participation in physical activities. Somewhat counterintuitively, a higher total intake of vitamin C was associated with prevalent dementia (odds ratio, 1.43; 95% confidence interval, 1.06 to 1.93). A trend toward a lower prevalence of dementia was seen in participants who spent 3 hours a day in nonphysical activities (odds ratio, 0.60; 95% confidence interval, 0.35 to 1.06). It is premature, however, to draw conclusions from these results. Studies of risk factors in incident cases of dementia are underway.

## 8. Translational research, and sharing our scientific resources

The call for translational research is a call for us to develop new approaches to investigating the challenges of human health. It is overly simplistic to look at a single vitamin, pathologic feature, or lifestyle factor in relation to AD. We require new paradigms and collaborations to take advantage of the wealth of information and recent scientific and technological advances. As we work to develop new quantitative approaches and new designs for clinical trials in this age group, we invite collaborations. We have built significant scientific resources for sharing data, including large repositories of well-characterized brain tissues, extracted DNA, cell lines, and clinical data. The 90+ Autopsy Study has enrolled 155 participants, and 91 autopsies have been completed. Samples of DNA have been collected from >500 participants. To request samples or propose a collaboration with our study, contact our Resource Sharing Coordinator via e-mail (mcorrada@uci.edu). As Leon Thal knew, it will take a village to meet this challenge.

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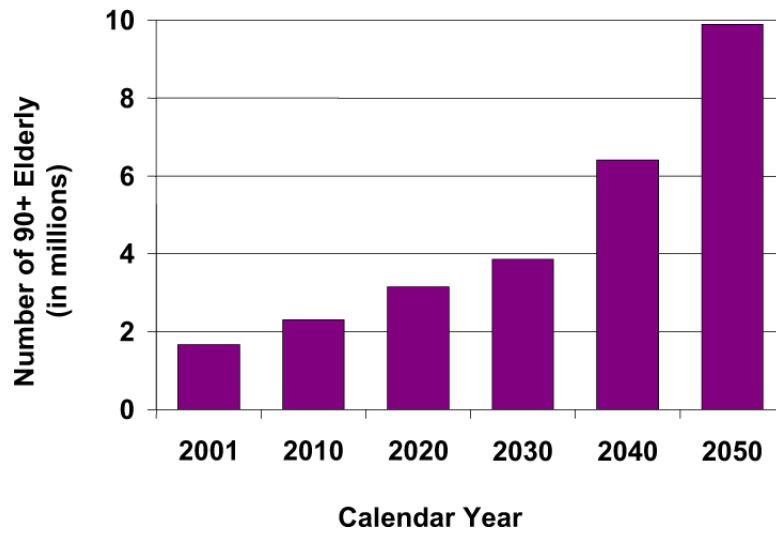
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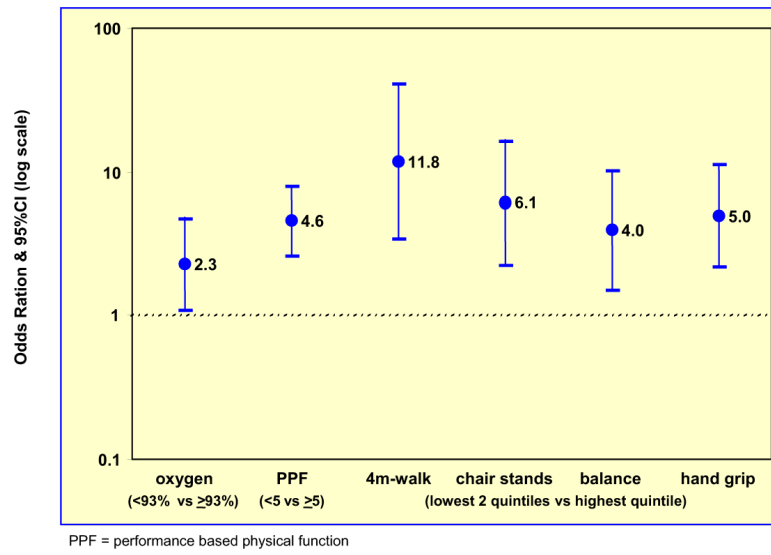
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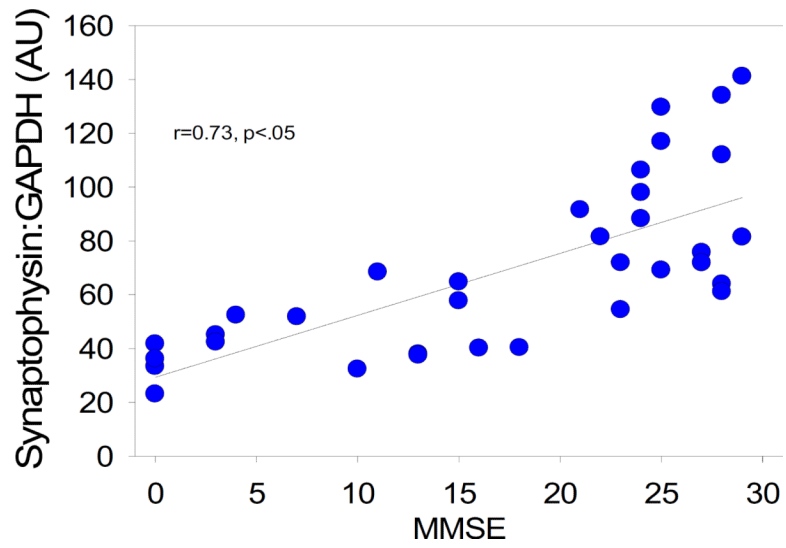


**Fig 1.**  
Projected United States population growth among 90+-year-olds.



**Fig 2.** Odds ratios of dementia for several variables of interest in the 90+ Study.





**Fig 3.** Correlation between frontal cortex synaptophysin protein level and Mini-Mental State Examination score in the oldest-old.