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Good morning. I am Dr. David Snowdon and I am a Professor in the Department of Neurology and the Sanders-Brown Center on Aging at the University of Kentucky Medical Center. I am the director of the Nun Study, a longitudinal study of health and aging.

I am delighted to be here with the School Sisters of Notre Dame – not just to describe some of the important findings of our study, but also to emphasize how important this type of long-term research investigation is to solving the enigma of Alzheimer's disease, and to urge you to find some way to keep this critical work going forward – as fast as possible.

Prevention depends upon understanding risk factors and how we can protect against them. To do that, we usually follow a population of people over a time and see who develops disease and who doesn't. After conducting a pilot study of Minnesota nuns in the 1980s, the staff of the National Institute on Aging encouraged us to submit a grant application to expand the Nun Study to all older School Sisters of Notre Dame throughout the U.S., including those living in Minnesota, Wisconsin, Illinois, Missouri, Maryland, Connecticut, and Mississippi. The institute funded our study in 1990, and it has been ongoing ever since.

Three factors made this religious population a rich source of research data and biologic material. First, this is a community whose members have had shared a common environment and lifestyle from early adulthood—which holds many confounding factors relatively constant. Second, each convent has an archive of information on each sister, from the time she entered the congregation as a young woman until her death. The archives provide a unique window into the early and middle lives of the sisters, decades before any of them developed Alzheimer's disease.

The third critical element is the courage and altruism of this inspired group of women, all of whom agreed to donate their brains at death for our studies. This allowed us to investigate risk and protective factors by comparing the brain tissue of cognitively-intact sisters to those who had severe symptoms of Alzheimer's, and every shade of grey in between these extremes. The 678 nuns in our study agreed to give us complete access to their historic personal and medical records, and participate in annual

examinations of the mental and physical function. We have followed them meticulously since 1991 and to date almost 500 brains have been donated by these carefully studied women—making it one of the world's largest neuropathologic studies.

Participants in our study range in age from 75 to107 years old. Sister Genevieve Kunkel from our Baltimore convent, who is sitting with me today, is one of our stellar examples from the study. She has avoided Alzheimer's and aged in a truly healthy and beautiful manner. Sister Genevieve describes healthy aging as being "alert and vertical"—in her comments at the end of my presentation you will witness the human potential available to all of us in a world without Alzheimer's.

I would like to underscore that this has been an interdisciplinary effort at the University of Kentucky – involving social scientists, anthropologists, molecular biologists, pathologists, and physicians. As we have progressed to more sophisticated questions, we are increasingly engaging scientists from other research institutions and other scientific disciplines. To maximize the federal government's and the sisters' investment in this study, we are making our rich source of data and tissue available to researchers across the U.S.

The Nun Study represents a long-term investment by the Federal Government. Since 1990, we have received 12 million dollars from the National Institute on Aging. Has the investment been worth it? You be the judge.

i. We were the first study to show how a preventable disease like stroke can trigger the symptoms of dementia in a person with an Alzheimer-brain.

ii. We were one of the first studies to show that deficiency in the vitamin Folic Acid appears to accelerate the brain-damaging effect of Alzheimer's disease.

iii. We were one of the first studies to show that Alzheimer's, like cancer and heart disease, is a life-long disease process. While it has been known for decades that low education is a risk factor for Alzheimer's, it has not been know why—is it related to early brain and cognitive development, a higher prevalence of lifestyle risk factors, or reduced access to health care in those with low education? Early cognitive development is likely to be a primary explanation. Linguistic analyses of autobiographies written by the nuns in early life indicates that low verbal skills are a potent predictor of Alzheimer's pathology in the brain and Alzheimer's symptoms 60 years after the autobiographies were written.

And this is only the beginning. We still have a great deal more to do.

We continue to pursue other novel approaches to the study of Alzheimer's disease. For example, over 95% of people will develop the protein deposits, the so-called plaque and tangle lesions of Alzheimer's, if they live to be old enough. Yet most will somehow escape showing any significant symptoms of this disease. We and other

scientists are trying to get a better understanding how such people avoid symptoms despite having the disease present in their brain.

We are also carefully studying the small minority of participants who never show the development of any significant Alzheimer's lesions—people who truly inhabiting a pristine world without Alzheimer's. Once we understand that, we'll be in a much better position to develop preventive interventions.

If we can attain additional funding in the future, the long-term investment by the National Institute on Aging will provide even more added-value:

i. For example, with nearly 500 brains in hand we are now working with world-renowned experts in the study of blood vessel diseases. This will allow us to get a better understanding of how the health and disease status of microscopic, small, and large blood vessels in the brain are related to Alzheimer's, other dementias, overall health and function, and longevity. By sharing brain tissue and data already collected on nearly 500 study participants with scientists at other U.S. research institutes, our colleagues there will have the ability to quickly and inexpensively perform new promising investigations that would otherwise cost literally 10's of millions dollars and take 10 to 20 years to complete. With only a couple millions dollars of funding, we can have the answers within a few years.

ii. Working with scientists at the University of Kentucky, Johns Hopkins University, and the University of Minnesota, we are now pursuing a strategy to use the genetic material collected from these nuns to ultimately create a genetic library for each of the 678 study participants. That is, the complete genome of each sister, all 30,000 plus genes, will ultimately be described and available in a computer database. If this study is funded, instead of going to the laboratory to study a single gene, investigators will simply log onto to the Nun Study Genetic Library to access the entire genetic structure of each sister, as well as all the risk factor data, medical history, and findings from the brain autopsy.

Since we began the Nun Study, we have seen an explosion in medical and scientific technology and methods, which has opened up enormous new opportunities for discovery. When we began, in 1991, we asked the sisters to donate some blood for future studies. At the time, we envisioned looking at nutrients and other chemicals in the blood, and possibly a gene or two. Never would we have imagined that development of technologies like gene amplification and micro-array analysis would allow us to determine the entire genome of individual sisters; or that we would need sophisticated data storage and data analyses techniques to handle this mind-boggling amount of genetic information. All of these add value to what we started, but, they all cost money.

The Nun Study is just one example of how the National Institute on Aging has capitalized on a long term funding strategy to provide a unique perspective on aging and Alzheimer's disease. Other investigators are pursuing unique populations, and there is much that remains to be done, especially in the study of dementia in specific

racial and ethnic populations—an area of study that at best, we have only rudimentary understanding.

We cannot put these studies off years and decades into the future. We need to conduct them now. There is still time to find answers and get interventions in place before the disease progresses further in the baby boomers, and subsequent generations. With only a minimal increase in National Institutes of Health funding this year, our research team and others across the U.S. will be stalled in our search for vital information about the prevention and treatment of this devastating disease. I urge Congress to find a way to make the commitment to finish the job it started. A world without Alzheimer's is within our grasp.

Now I would like to ask Sister Genevieve Kunkel, one of our participants in the Nun Study, to add some brief comments.