

*The Danish 1905 Cohort:*  
*A Genetic-Epidemiological Nationwide Survey*

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**Objectives:** The authors studied nonagenarians, a rapidly growing age group whose cognitive and physical abilities have yet to be investigated systematically. **Methods:** All Danes born in 1905 were invited to participate in a home-based 2-hour multidimensional interview, including cognitive and physical performance tests and collection of DNA, carried out by lay interviewers. Population-based registers were used to evaluate representativeness. **Results:** There were 2,262 participants. A total of 1,632 (72%) gave a DNA sample. Participants and nonparticipants were highly comparable with regard to marital status, institutionalization, and hospitalization patterns, but men and rural area residents were more likely to participate. Six months after the survey began, 7.2% of the participants and 11.8% of the nonparticipants had died. **Discussion:** Despite the known difficulties of conducting surveys among the extremely old, it was possible to conduct a nationwide survey, including collection of DNA, among more than 2,000 fairly nonselected nonagenarians using lay interviewers.

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*The Danish 1905 cohort study* is a nationwide survey of all Danes born in 1905. The overall goal is to establish a genetic-epidemiological database to shed light on the aging process among the extremely old.



We wanted to describe the extremely old, focusing on physical and

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cognitive functioning, and to examine the feasibility of using lay interviewers to test physical functioning and to collect DNA.

Since the 1950s, the mortality rate among the oldest old in the developed countries has declined dramatically (Vaupel et al., 1998), causing a big rise in the number of oldest old (80+ years). Whereas both centenarians and octogenarians are by now relatively well described, only a limited number of smaller surveys focusing on nonagenarians has been conducted (Forsell, Jorm, von Strauss, & Winblad, 1995; Harris, Finucane, Healy, & Bakarich, 1997; Heeren, Lagaay, von Beek, Rooymans, & Hijmans, 1990; Meller, Fichter, Schroppel, & Beck Eichinger, 1993; O'Connor, Pollitt, Brook, & Reiss, 1989; Ravaglia et al., 1997). Although many of the cross-sectional and longitudinal population-based studies of the elderly include nonagenarians, data on this group are seldom presented separately, possibly due to the small number participating. Furthermore, most of the ongoing longitudinal surveys of younger elderly will not provide information on the extremely old (90+ years) because the majority of the study population will have deceased before they reach the extreme ages. The present study has bypassed these problems by conducting a nationwide survey among 2,262 nonagenarians. Five percent of the cohort is expected to live to be 100 years old, which will provide sufficient power to allow detailed studying of a large number of predictive factors for loss of abilities and mortality/survival in the follow-up surveys. In this article, the method, study population, and feasibility of the study are described.

### *Participants and Methods*

The only inclusion criteria in the survey was that the participants were born in 1905 and living in Denmark. All nonagenarians from this birth cohort were approached irrespective of residence, health, and cognitive status. Nonagenarians living in institutions were also approached. There were no exclusion criteria.

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The small size of the country (5.3 million inhabitants, 43,000 square km) and the extensive registration of the inhabitants make Denmark an attractive setting for population-based studies. All inhabitants have a 10-digit unique and permanent personal identification number, which includes the date of birth and gender of the person (ID number). The ID numbers are recorded in the Danish Civil Registration System (DCRS), along with demographic information, including date of death. In early 1998, we retrieved data on ID numbers, names, addresses, and marital status of all Danes living in Denmark who were born in 1905. Hence, eligible participants were 92 or 93 years of age at the time of the survey. The survey was approved by the Central Scientific Ethical Committee of Denmark.

All persons in the cohort received a letter explaining the study and asking permission for an interviewer to come to their residence to conduct a health-related, face-to-face interview and test their mental and physical functioning. They were also asked to give a sample of cells from which DNA could be isolated. If the person was unable to participate due to physical or mental impairment, a proxy responder was encouraged to participate in the interview instead. The nonagenarians were contacted within 14 days by the interviewer, either by personal contact or by phone, to obtain consent to participate in the survey.

The nonagenarians were considered nonparticipants if they did not wish to participate in person or by proxy or if at least three attempts to contact them, at different times, were unsuccessful.

During a 3-month period in 1998 (August to October), 93 interviewers from the Danish National Institute of Social Research carried out the survey. The interviewers are not medically or paramedically trained but do, however, have substantial experience in interviewing the elderly (Christensen, Holm, McGue, Corder, & Vaupel, 1999). All interviewers received a detailed training program by physicians just before the start of the survey and were closely monitored during the interview period.

A pilot study was performed in the spring of 1998, composed of a total of 200 persons from the 1905 cohort. This study resulted only in minor changes of the interview, and these data are included in the overall analysis.

The interview part of the survey took, on average, 1 1/2 hours to perform. Questions concerning the following topics were asked:

Sociodemographic factors: living conditions, educational attainment, and work.

Anthropometric measures: self-reported height and weight (current, at age 25, maximal weight ever).

Lifestyle habits: previous and current smoking and drinking behavior.

Health: self-rated health, diseases diagnosed by a physician, symptoms of pulmonary and heart diseases, incontinence, pain, fall events, and fractures. All drugs, vitamins, and alternative medications taken on a regular basis were recorded.

Physical ability: Avlund's physical activity of daily living scale (Avlund et al., 1991), Questions from Katz's ADL scale (Katz et al., 1970) and from Nagi's measures of functional limitations (Nagi, 1976).

Psychological status: Symptoms of depression were measured by a modified scale from the Cambridge Mental Disorders of the Elderly Examination (McGue & Christensen, 1997; Roth et al., 1986). An informant questionnaire (DECO) (Ritchie & Fuhrer, 1992) was used for evaluation of cognitive impairment in the proxy interview.

Sensoric deficits: self-reported hearing and vision impairments.

Family history: parents' age at death, participant's age at birth of first and last child.

Social life: contacts with friends and family, participation in social activities.

The questionnaire, with minor changes, has previously been used in the Longitudinal Survey of Aging Danish Twins (Christensen et al., 1998; Christensen et al., 1999; McGue & Christensen, 1997).

Participants not able to participate in the face-to-face interview participated through a proxy responder; in most cases, this was a close relative who went through a questionnaire identical to that used in the face-to-face interviews.

Testing of cognitive and physical functioning lasted approximately 30 minutes. The following tests were included:

Cognitive abilities: Mini Mental State Examination (M. F. Folstein, S. E. Folstein, & McHugh, 1975), verbal fluency, forward and backward digit span, and immediate and delayed recall of 12 words.

Physical performance: ability to lift a 2.7 kg box above the head, flexibility (ability to bring hands to neck, loin, and opposite toe), single chair stand with or without the use of arms, and timed walk over a distance of 3 meters. These tests were, with minor changes, performed according

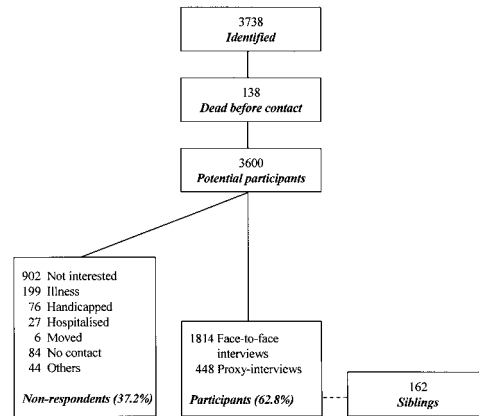
to the protocol from the Women's Health and Aging Study (Guralnik, Fried, Simonsick, Kasper, & Lafferty, 1995). Handgrip was tested using a handheld dynamometer (SMEDLEY'S, dynamometer TTM) for three performances with the strongest hand. Pulmonary function was measured using a small digital spirometer (MicroDL, Micro Medical Wtc) among approximately half of the participants who were living in the western part of the country. Because we did not have sufficient funds to purchase digital spirometers for all 93 interviewers, participants living in the eastern part of the country had their pulmonary function tested using a peak-flow meter (Mini-Wright).

The DNA sample could either be given as a bloodspot or as a cheek swab. The participants were asked to prick a finger with a special sterile automatically retractable lancet (Tenderfoot<sup>®</sup> ICT, USA). Bloodspots were then collected on filter paper. Approximately 5 square cm of the filter paper was soaked with blood. A bloodspot was defined as having a poor quality if no more than 1 square cm of the filter paper was filled with blood or not soaked through. Alternatively, DNA was sampled by a swab from the inner side of the cheek. The swabs were received in the laboratory within 24 to 48 hours after collection.

Participants and nonparticipants were compared with regard to sex, marital status, type of housing, and area of residence (rural/urban) using data from the DCRS. Data from this registry were also used to estimate the mortality in the two groups 6 months after the start of the survey.

Information on hospital discharges was available from a population-based register with complete coverage of Funen County (approximately 9% of the Danish population) for the period from 1973 to 1998. We retrieved data on all 1905 cohort members residing in the county ( $n = 398$ ), and we calculated the total length of hospital stays and number of discharges during the 26-year period prior to the study for participants and nonparticipants. The two groups were also compared for hospitalization in 1998 as a marker of recent decline in health.

Siblings were identified by asking participants who gave DNA if they had any brothers or sisters older than 88. The siblings were then contacted in the same manner as described above and went through the same questionnaire, tests, and collection of DNA.



**Figure 1.** The ascertainment of participants from the Danish 1905 cohort survey.

## Results

A total of 3,738 people were alive at the beginning of the recruitment period, but 138 died before being contacted, leaving a total of 3,600 potential participants (see Figure 1). Of these, 2,262 (62.8%) consented to participate in the study—1,814 (80.2%) by person and 448 (19.8%) by a proxy respondent. The reasons for using a proxy respondent were dementia (57.0%), severe sensoric deficits (14.1%), unwillingness to participate personally (14.1%), and illness (13.9%). In most of the proxy interviews (77.9%), a first-degree relative was interviewed. Most (86%) of the proxies saw the nonagenarian at least once a week.

Face-to-face interviews were conducted with the nonagenarian alone in 81% of the cases, and in 19% of the cases, another person participated together with the nonagenarian, most often a child (49.9%) or a spouse (16.8%). The interviewers considered the face-to-face interview as easy to conduct in 64% of the cases, somewhat difficult in 26% of the cases, and difficult in 10% of the cases. Problems with hearing (33%), vision (24%), and cognitive impairment (10%) were the most common causes that impeded the interview.

There were 1,338 (37.2%) nonparticipants. Males were more likely to participate than females (68.9% vs. 61.0%;  $\chi^2$  test,  $p < 0.001$ ) (see Table 1). There was no difference in residence type or marital status

Table 1  
*Demographic Characteristics at Baseline and Postsurvey Mortality of the 1905 Cohort in Denmark*

	<i>Participants by Person (n = 1,814, 50.4%)</i>		<i>Participants by Proxy (n = 448, 12.4%)</i>		<i>All Participants (n = 2,262, 62.8%)</i>		<i>Nonparticipants (n = 1,338, 37.2%)</i>		<i>Total (N = 3,600, 100%)</i>	
	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>
Number of participants (% of sample)	494 (27.2)	1,320 (72.8)	90 (20.1)	358 (79.9)	584 (25.8)	1,678 (74.2)	265 (19.8)	1,073 (80.2)	849 (23.6)	2,751 (76.4)
Sex ratio (female:male)	2.67		3.98		2.87		4.05		3.24	
Type of residence										
House/apartment	300 (60.7)	757 (57.3)	21 (23.3)	77 (21.5)	321 (55.0)	834 (49.7)	142 (53.6)	547 (51.0)	463 (54.5)	1,381 (50.2)
Sheltered housing/ nursing home	180 (36.4)	550 (41.7)	64 (71.1)	279 (77.9)	244 (41.8)	829 (49.4)	115 (43.4)	503 (46.9)	359 (42.3)	1,332 (48.4)
Other	14 (2.8)	13 (1.0)	5 (5.6)	2 (0.6)	19 (3.3)	15 (0.9)	8 (3.0)	23 (2.1)	27 (3.2)	38 (1.4)
Area of residence										
Rural (less than 500 participants per square km)	351 (71.1)	855 (64.8)	67 (74.4)	255 (71.2)	418 (71.6)	1,110 (66.2)	176 (66.4)	557 (51.9)	594 (70.0)	1,667 (60.6)
Urban (more than 500 participants per square km)	143 (28.9)	465 (35.2)	23 (25.6)	103 (28.8)	166 (28.4)	568 (33.8)	89 (33.6)	516 (48.1)	255 (30.0)	1,084 (39.4)
Marital status										
Widow/widower	318 (64.4)	1,068 (80.9)	54 (60.0)	297 (83.0)	372 (63.7)	1,365 (81.3)	140 (52.8)	853 (79.5)	512 (60.3)	2,218 (80.6)

Divorced	12 (2.4)	51 (3.9)	—	16 (4.5)	12 (2.1)	67 (4.0)	7 (2.6)	54 (5.0)	19 (2.2)	121 (4.4)
Married	140 (28.3)	44 (3.3)	31 (34.4)	12 (3.1)	171 (29.3)	56 (3.3)	99 (37.4)	29 (2.7)	270 (31.8)	85 (3.1)
Single	24 (4.9)	157 (11.9)	5 (5.6)	33 (9.2)	29 (5.0)	190 (11.3)	19 (7.2)	137 (12.8)	48 (5.7)	327 (11.9)
Postsurvey mortality <sup>a</sup>	31 (6.3)	55 (4.2)	20 (22.2)	55 (15.4)	51 (8.7)	110 (6.6)	38 (14.3)	120 (11.2)	89 (10.5)	230 (8.4)

*Note.* Percentages in parentheses.

a. Within 6 months after the start of the survey.

Table 2  
*Hospital Discharge Registry Information on  
 Eligible Participants From the 1905 Cohort Living in the County of Funen*

<i>Hospital Discharges</i>	<i>Participants (n = 283)</i>	<i>Nonparticipants (n = 106)</i>	<i>Total (N = 389)</i>
Number of hospital discharges from 1973 to 1998, median (range)	4 (0-19)	3 (0-17)	3 (0-19)
Total number of days in hospital from 1973 to 1998, median (range)	38 (0-299)	33 (0-265)	37 (0-299)
Number of persons hospitalized in 1998 (%)	85 (30.0)	35 (33.3)	120 (30.8)

among participants and nonparticipants ( $\chi^2$  test,  $p = 0.19$ , 0.13). As expected, participants interviewed by proxy were more likely to live in nursing homes. In all groups, females were more often nursing home residents and bereaved of their spouses. Participants living in urban areas (more than 500 persons per square km) were more likely to be nonresponders ( $\chi^2$  test,  $p < .001$ ), especially in the metropolitan area of Copenhagen, where only 49% participated. Male participants were more frequently widowers than were male nonparticipants ( $\chi^2$  test,  $p = 0.003$ ).

The total death rate within 6 months was 8.9%. Mortality among nonparticipants (11.8%) was higher than among participants (7.2%) (log-rank test,  $p < .001$ ). Mortality was especially high among persons who refused to participate because of illness (18.6%) or hospitalization (44.4%). In all groups, the mortality among women was lower than among men.

Information from the hospital discharge registry of Funen County is shown in Table 2. Participants and nonparticipants were highly comparable with regard to the number of hospital admissions (Mann-Whitney test,  $p = .185$ ), total number of days in hospital in the previous 26 years (Mann-Whitney test,  $p = .58$ ), and admissions during 1998 ( $\chi^2$  test,  $p = 0.571$ ).

In all, 350 siblings to members of the 1905 cohort were eligible for inclusion. The nonagenarians allowed us to contact 283 of them, and we were able to trace 227 persons; 162 siblings (71.4%) participated.

A total of 1,639 (72.5%) participants from the 1905 cohort gave a sample of DNA: 1,317 (80.4%) by means of blood spots and 322

(19.6%) as cheek swabs. Most of the blood spots—1,201 (91.8%)—were classified as being of good quality. Every third cheek swab was tested with a Polymerase Chain Reaction, revealing a fragment of 250 base pairs on all, indicating good quality of the DNA. In all, 137 (84.5% of the interviewed) siblings gave a DNA sample.

### *Discussion*

The survey of the 1905 cohort has shown that it is possible to conduct a large-scale genetic-epidemiological survey among extremely old people in Denmark. To the best of our knowledge, a survey of a national cohort of nonagenarians, including physical and cognitive tests and collection of DNA material, has never been conducted before.

Comparisons of cross-sectional studies of octogenarians and centenarians indicate dramatic increases in the frequency of nursing home admissions and in the occurrence of impairments, disability, and morbidity across these age groups. However, nonagenarians represent an age group whose cognitive, physiological, and physical features have yet to be investigated systematically. We find nonagenarians very important to study for several reasons. A large degree of heterogeneity with respect to both physical and cognitive functioning can be expected among nonagenarians, and levels of functioning will often tend to decrease rapidly as the nonagenarians age. Compared to centenarians, nonagenarians are more functionally active and therefore more able to participate in a survey and to carry out the test battery. Therefore, following nonagenarians over time may provide more valuable information than following centenarians. Furthermore, what can be learned from nonagenarians may be more generalizable to the total older population than what can be learned from the very rare and selected group of centenarians. We believe that the follow-up studies of this age group within a few years can be expected to shed some light on the aging process among the extremely old.

Studying the oldest old is a very complex issue; a major concern is to maximize the participation rate (Simonsick et al., 1997). We took several initiatives that have been reported to improve response rates (Lundberg & Thorslund, 1996; Rodgers & Herzog, 1992). The letter inviting the nonagenarians to participate in the survey was carefully

composed and written in a large font. It was stressed that the survey was home based and that participants could participate in the survey without giving a sample of DNA. Furthermore, we encouraged proxies to participate together with or instead of the participant. The interviewers were well trained and motivated and made great efforts to include the potential participants in the survey. Additional information letters were sent to the caregivers of the nonagenarians. Despite these initiatives, the participation rate was not very high (62.8%). Several factors may have contributed to the lower participation rate in our study compared to other surveys. First of all, identification of eligible participants in previous studies may have been incomplete due to lack of registration of the population and to age-validation problems (Hoinville, 1983; Rodgers & Herzog, 1992). In Denmark, we have a complete and valid registration of the entire population. Second, in contrast to many population-based surveys where people with severe cognitive or sensory impairments are excluded, no exclusion criteria were used in the 1905 cohort survey to enhance representativeness.

Population-based studies of people age 90 and older with good participation rates have been reported in the literature (Forsell et al., 1995; O'Connor et al., 1989; Steen & Djurfeldt, 1993). However, they are characterized by having been conducted in relatively small areas with a limited number of participants and by using physicians or nurses for the examination. This probably makes potential participants more committed to the survey and therefore less likely to be nonresponders. Larger surveys of elderly have response rates similar to ours (Ebly, Parhad, Hogan, & Fung, 1994).

Therefore, considering the valid identification of the entire 1905 cohort, the lack of exclusion criteria, the size of the study, and the age, morbidity, and disability level of these extremely old people, we find the relatively low participation acceptable.

In the 1905 cohort survey, we evaluated differences between participants and nonparticipants with valid register-based data. We found no differences in marital status or housing type, but men and participants living in rural areas were more likely to participate, which are findings common to other studies of elderly people (Christensen et al., 1999; Ganguli, Mendelson, Lytle, & Dodge, 1998; Sørensen, Sivertsen, Schroll, & Gjørup, 1982). Analyzing hospitalization patterns did not indicate that responders were more healthy than nonresponders, as

hospitalization patterns in the 26 years preceding the survey and in 1998 showed no difference between the two groups. However, in a 6-month period after the start of the survey, nonresponders had higher mortality, indicating that terminal illness was one of the reasons for nonparticipation. The higher nonresponse rate in the urban areas was not caused by a higher mortality among persons living there compared with persons living in rural areas; the mortality rate in urban areas was 10.8% versus 15.4% in rural areas. Furthermore, the Danish population of elderly is very homogenous with respect to ethnicity and social conditions. We think these circumstances provide support for regarding the survey as reasonably representative of the population of the oldest old. In certain parts of the country, the participation rate was high (up to 73%), and it is possible to stratify on residency when analyzing the data and thereby have an additional test of the representativeness of the overall sample.

A substantial proportion of the oldest old is incapable of providing accurate responses to survey questions or even participating in the interview due to cognitive impairment or frail health (Rodgers et al., 1992). This necessitates the frequent use of proxy responders, as seen in the present study. The literature on proxy information in epidemiological surveys suggests that validity varies considerably depending on the type of information sought (Rodgers et al., 1992) but can be improved by using different kinds of proxies (Lundberg & Thorslund, 1996). In our study, a substantial proportion of the participants (19.8%) were interviewed by proxy. The proxies knew the participant very well (86% saw the participant at least once a week), and furthermore, the interviewers were instructed to contact caregivers if there were any questions concerning medication or ADL that the proxy was unable to answer.

When choosing instruments for the survey, we had to take into consideration that the survey was home based and that the interviewers had no medical background. Furthermore, the length of the visit should be limited to no more than 2 hours, because very old people get tired easily, which probably could impair the quality of information retrieved.

Physical performance measures were included in the study to provide objective and detailed information about functional capacity to understand the pathway from pathology to disability. However, the

expected high prevalence of disabilities and sensory deficits makes many of the instrument batteries developed for studies of younger elderly unsuitable for use in a cohort of very old people (Olsen, Jeune, & Andersen Ranberg, 1996; Ravaglia et al., 1997). The physical performance tests were therefore carefully selected in consideration of the age and expected functional capacity of the study population. The majority of the participants could perform the tests, and no accidents occurred.

Twin studies indicate that the influence of genes increases with age for a number of important attributes (McClearn et al., 1997). Comparison of DNA from the oldest old with DNA from younger individuals is among the design options for identifying genes that are of importance for the aging process and life span. To make future genetic studies feasible, DNA from the nonagenarians and their siblings was collected. The majority of the participants were willing to give a sample, and the DNA was of good quality. The relatively low participation rate in the survey will only represent a bias problem in a prevalence study if the genetic factors studied are associated with both nonparticipation and the outcome of interest but not for follow-up studies within the response group. The "affected sib pair design" ("affected" for longevity), which we intend to use, is robust against selection problems because this design intends to identify families with more than one case (here, two siblings) (Khoury, Beaty, & Cohen, 1993).

In conclusion, despite the known difficulties of conducting surveys among the extremely old, the Danish 1905 cohort survey shows that it is feasible to conduct a nationwide genetic-epidemiological survey, including collection of DNA, among nonagenarians. The large and fairly nonselected sample of interviewed persons provides a unique research resource for describing the population of nonagenarians and for studying environmental and genetic determinants of loss of abilities and mortality, thereby helping to elucidate the aging process.

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