# Methodological issues in centenarian research: pitfalls and challenges

**SPECIAL ARTICLE** 

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#### **ABSTRACT**

Assumptions based on findings from younger individuals are not necessarily true for centenarians. It is important to establish appropriate research questions for this age-group. Research with these individuals poses some methodological challenges. The challenges vary for biophysical, psychosocial or ethnographic research. In selecting a representative sample, the main challenges are problems of identification, verification of age, motivation of gatekeepers, frailty, cognitive impairment, high morbidity and mortality rates, and frequent withdrawals from research owing to ill health. Study designs may be cross-sectional or longitudinal, quantitative or qualitative, cohort or case-control, depending upon the research objectives. Issues of age verification, appropriate measurement tools, reliance on third parties, and other challenges are common. Current and future studies must address these methodological pitfalls to maximise the generalisability of findings. This paper provides an overview of these challenges for cross-sectional and longitudinal designs in centenarian research.

Key words: Aging; Longevity; Research design

#### INTRODUCTION

In 2009, the United Nations estimated that there were 455 000 centenarians in the world,<sup>1</sup> with the number increasing at a faster rate than any other segment of the population.<sup>2</sup> Centenarians are considered as exemplars of longevity and healthy ageing, and epidemiological research has been conducted to look at the various health events and health characteristics of successful ageing in this population. These studies may help discover factors that protect an individual from age-related diseases, in particular cognitive disorders. A greater understanding of their patterns of service use will assist health planners and economists to better plan health services for the future and make them more responsive to the needs of the elderly.

Studies of centenarians from the US,<sup>3,4</sup> Japan,<sup>5</sup> France,<sup>6</sup> Italy,<sup>7</sup> Hungary,<sup>8</sup> South Korea,<sup>9</sup> Finland,<sup>10</sup> Denmark,<sup>11</sup> Sweden,<sup>12</sup> and Australia<sup>2</sup> have been reported. Some of the methodological challenges identified are shared by studies of older individuals, but others are unique to this population. This paper provides an overview of these challenges for cross-sectional and longitudinal designs in centenarian research.

# **CONCEPTUAL FRAMEWORK**

Centenarians are of exceptional longevity.<sup>13</sup> In most countries, the distribution of age at death is near normal,

with a thick left tail largely attributable to early life mortality. This has rapidly shrunk in developed societies and is now decreasing in all societies.14 The mean age of death has increased consistently, thereby shifting the curve to the right, and there has been some convergence of unconditional variances in the age of death in industrialised societies. If centenarians are those few individuals who happen to lie in the right tail of this distribution, does this make them unique? Should the study of exceptional longevity therefore be based on statistical measures, such as 3 or 5 standard deviations above the mean? Studies of exceptional longevity must critically examine these questions. Some 'centenarian' studies consider that it is not necessary for the participants to be centenarians in order to examine determinants of exceptional longevity. For example, the Sydney Centenarian Study enrolled individuals over the age of 95 years; the Heidelberg Centenarian Study<sup>15</sup> included individuals after their 99th birthday with the expectation that they would reach 100 years of age; a Swedish study investigated dementia and stroke in 97-year-olds16; and a Californian study of exceptional ageing began at age 90 years.<sup>17</sup>

Even if centenarians are considered to be outliers, are all centenarians outliers, or only those who have reached an extreme age in relative good health or with some special characteristics? To some extent this is determined by the objectives of the investigation. For example, a study of the protective factors against dementia may focus on

centenarians with preserved cognition, 18 or compare those with and without dementia. A study of the genetics of longevity may investigate centenarians who have a family history of exceptional longevity19 or compare long-living twins.20 Appropriate sampling enables investigation of a representative sample. Published studies have used diverse sampling and verification methods, each with its own set of challenges. In addition, there are difficulties in assessing and measuring the physical and mental health of very old people. Different studies of health behaviours, lifestyle, and environmental factors apply different approaches when studying the physical health of centenarians.

## **METHODOLOGICAL ISSUES**

## Verification of age

Accurate determination of age is of paramount importance. The challenges of validating age in centenarian studies have been described.<sup>21</sup> The claims of 150-year-old individuals in the Russian Caucasus, Hunza Valley in Pakistan, or Vilcabamba in Ecuador have been shown to be age exaggeration for various reasons. Only a few countries had good maintenance of accurate birth records over a century ago. In the state of Georgia, US, birth certificates were not issued until 1928.22 In addition, it takes time to verify a person's age. For example, in the case of Madame Jeanne Calment, who holds the Guinness World Record as the oldest-ever person in the world, having died at the age of 122 years and 164 days in 1997, age verification by the Ipsen Foundation took over a year. Her birth certificate was on file at the Arles Public Library but researchers had to ascertain whether she was indeed the person named on the birth certificate. Self-report of age or date of birth is not sufficient evidence for this purpose. Unfortunately, census data in many countries, such as Australia and the United States, rely on self-report of age. The Japanese Health and Welfare Bureau for the Elderly has more accurate data, but inaccuracies have also been reported.23 The recommended approach, therefore, is to not rely on one source of information, but to use multiple, convergent and validated sources, such as birth certificates, early school records, marriage certificates, children's birth certificates, passports, etc. Guidelines for this have been published.<sup>24</sup>

# Obtaining an optimal sample

In convenience sampling, where subjects are selected because of their convenient accessibility and proximity to the researcher, centenarians usually are visible, proud of their longevity, keen to participate in research, high functioning, and able to complete the required assessments.25 Some countries hold special events to celebrate their long-living citizens, and this is one source of recruitment for studies. Another approach is recruitment by advertisement, which is likely to be read only by those who are well functioning and/or supported. Other strategies used include culling names from the media, approaching local agencies and older citizens' organisations, word-of-mouth advertising, etc. Such samples lack generalisability of the results, as participants are on average healthier, both physically and cognitively, than the general population of that age and may be regarded as 'expert survivors'. It is estimated that about 70% of centenarians do not fall within a high-functioning, homogeneous group.<sup>26</sup> Comparison of the oldest-old cohort to controls with similar inclusion criteria except younger in age may provide insights.<sup>25</sup> Generalisation of the findings to the overall population of centenarians would be limited to the better-functioning oldest old. When multiple cohorts are used for comparison, the potentially confounding cohort effects also need to be considered. For certain purposes, convenience sampling is the only feasible approach. For instance, a study of neuroimaging of centenarians may recruit participants who are healthy, able to consent to the procedure and tolerate it, and live within a certain geographical area. Such a select sub-group can still address some important questions.

Most studies aim to obtain a representative sample of the general population, with broad distribution of cognitive abilities, living situations, and health and functional capacities. These studies include the New England Centenarian Study,4 the Georgia Centenarian Study,3 the Japanese Centenarian Study,<sup>27</sup> the Heidelberg Centenarian Study,<sup>28</sup> and the Sydney Centenarian Study. Nonetheless, it is difficult to locate all potential participants and ensure that they are representative of the general population.

There are various methods to achieve comprehensive sampling within a defined geographical area. The Heidelberg Centenarian Study<sup>15</sup> defined a geographical area of about 60 km<sup>2</sup> around the city and sampled 172 communities with 2.6 million inhabitants. Records were obtained from the resident registration offices on inhabitants born in 1901 or earlier and all potential participants were invited to participate in the study. However, a substantial portion of the data could not be verified or the individuals were deceased, thereby reducing the number of participants to 86 (46%) from a potential 179. The Georgia Centenarian Study<sup>3</sup> initially attempted to enlist Medicare enrolees, as more than 95% of older adults in the US are on the Medicare rolls. However, a change in administrative procedures did not permit this, and an alternative strategy had to be employed. The strategy employed had 2 components: (1) all registered voters aged ≥98 years in the area were contacted and (2) all skilled nursing facilities and personal care homes in the area were contacted for the identification of potential participants. The Sydney Centenarian Study used both the electoral roll and Medicare data, as Australia has a universal Medicare system. This did not produce a comprehensive sample and had to be supplemented with contacting all residential aged care facilities in the area of interest, together with recruitment through word-of-mouth, newspaper articles

and community forums, hospital admissions, and referrals by geriatricians and psychogeriatricians.

Despite efforts to achieve comprehensive coverage, a population-based study is rarely able to enrol all eligible participants, as research is voluntary. Many centenarians choose not to participate or are too impaired to give informed consent and their families are unwilling or unable to provide proxy consent. People who volunteer to be participants are generally higher functioning than the general population. Complete ascertainment is feasible if the population is geographically isolated and ethnically distinct, and the community is involved, such as in the Okinawan<sup>29</sup> and Sardinian<sup>30</sup> centenarian studies. Nonetheless, these studies may not yield findings that are readily applicable to other populations.

Representative population-based sampling enables comparing and contrasting differences in performance among centenarians with a wide range of cognitive abilities, living situations, health and functional capacities. The elderly included are not limited to those living in private households and cognitively intact, but rather include a substantial proportion of centenarians who are living in nursing homes and assisted living facilities due to significant cognitive and physical limitations. Representative samples enable examination of the genetic contribution to longevity, relationships between neuropathology and cognition, behavioural, health and disease contributions to function, and generalisation of the findings.

The representativeness of a sample can be checked by comparing its sociodemographic variables with that of the general population. If clinical characteristics (rates of some diseases or lifestyle) are also available, the comparison becomes more instructive. To deal with the lack of representativeness, weighting should be used for the unequal probabilities of selecting centenarians in different residential settings or age and sex, and the problem of non-response.31 The Georgia Centenarian Study<sup>3</sup> did this by using contemporaneous census data and performing post-stratification with respect to geographic substratum, age, sex, race, and type of residence. They stratified the data first on one of the 5 characteristics, readjusted on cross-tabulation of successive pairs of the other 4 characteristics, and repeated the steps until a stable set was achieved. This resulted in 4 weighted schemes: unweighted, untruncated weights, truncated weights, and adjusted truncated weights. A comparison of key variables under the 4 schemes suggested that the truncated weights at the 5th and 95th percentiles produced the most consistent results. Even if sampling weights are not used, knowledge of discrepancies between the sample and the larger population is helpful in the interpretation of the results.

# Selecting a comparison group

Whether exceptional longevity is associated with genetic

or environmental factors, comparison of centenarians with younger individuals of various age-groups is necessary. The Georgia Centenarian Study<sup>3</sup> recruited a control group of octogenarians, and the Sydney Centenarian Study compared centenarians with participants aged 70 to 90 years in the Sydney Memory and Ageing Study. It is important that the same sampling rigour is applied to the comparison groups. A younger comparison group has 2 disadvantages: (1) there may be significant cohort differences as the developmental and life experiences may differ; and (2) it cannot be ascertained whether some individuals in the control group will not go on to be centenarians. Ideally, a large cohort of individuals is followed up from birth until some of them become centenarians. Nonetheless, only 1 in 5000 individuals becomes a centenarian. In time-sequential studies, centenarians are compared with younger controls at one time point and then 20 years later such that enduring factors that influence exceptional longevity can be identified and cohort differences can be taken into account.

## Cross-sectional versus longitudinal designs

Cross-sectional designs are less resource intensive and can be completed in a short period. They reflect health status at a particular point in time (e.g. point prevalence of dementia, morbidity, quality of life, etc.), enabling comparison with a control group. They enable greater control over sample selection and measurement, permit the study of several factors and outcomes at the same time, and help generate hypotheses for examination in a longitudinal design. Most studies of centenarians tend to initially report on cross-sectional data. Phase 1 of the Georgia Centenarian Study<sup>3</sup> adopted this strategy when comparing the adaptation characteristics of community-dwelling, cognitively intact centenarians, octogenarians, and sexagenarians living in Georgia, US. The major disadvantage of cross-sectional designs is that causal inferences cannot be drawn from the observed associations, as exposure and outcome are measured at the same time. They do not yield incidence rates, and there are often sampling and/or survivor biases. Measurement, especially that reliant on recall, is also prone to bias. Moreover, cohort effects in addition to chronological age may influence the results.

A longitudinal study can overcome some of the limitations of the cross-sectional design. An ideal longitudinal study is to follow up a cohort over several decades, with the expectation that a small proportion of participants will reach exceptional old age. Nonetheless, such a study to examine risk and protective factors of ageing prospectively is prohibitively expensive and possibly impractical. A possible solution is to recruit an enriched sample, e.g. the offspring of centenarians who tend to have long lives (although this may reduce some of the genetic variability). A longitudinal component enables analysis of cognitive and physical status across time, including rates of decline and incident dementia.

One major limitation of such studies is the high attrition owing to mortality and morbidity increasing the effect of survivor biases. A strategy to overcome this problem is dynamic recruitment wherein individuals in younger age-groups (e.g. 99 years in the Heidelberg Centenarian Study, 98 and 99 years in the Georgia Centenarian Study, and 95-99 years in the Sydney Centenarian Study) are recruited with the expectation that a significant number will become centenarians. The intervals between followup assessments are an important consideration, as long intervals will lead to high attrition, whereas very short intervals lead to confounding owing to practice effects and insensitivity to change, and also run the risk of overwhelming the participants. Many studies mandate annual assessments, but shorter intervals, such as 6-monthly assessments in the Sydney Centenarian Study may help improve retention rates.

# Qualitative versus quantitative data

Understanding of culture and lifestyle are of great importance in successful ageing, and ethnographic methods are well suited to study these. A good ethnographer spends a great deal of time in sharing life and experiences with the subjects and develops insights by observation. These observations can serve as hypotheses for subsequent quantitative work. Such case studies have been carried out in Okinawa (Japan),32 Chejudo (Korea),33 and Sardinia (Italy),<sup>34</sup> among others. Factors that promote longevity have been identified, including a low calorie diet, work ethic, optimism, and large social networks. Some of these have been substantiated using the quantitative method.

## Difficulties of measurement in centenarians

Assessments are often carried out in the centenarian's home, as he/she may have frailty, cognitive deficits, mobility problems, sensory impairment, etc. A visit to the home also offers an opportunity to assess the participant's lifestyle and activities of daily living. Very old people may be suspicious of strangers and their motives. Assessment in their own home offers them security and ease in involving family members, but involves an additional expense. Family and friends of centenarians may act as gatekeepers for any research participation, and therefore involvement of a family member is important in the research process, even when the centenarian is autonomous and fully competent to participate independently. The wishes of family members (e.g. no brain scan or blood taken) should generally be acceded to, unless this significantly compromises the research, and the participant is fully competent and engaged enough to reject the family's wishes.

Assessment of centenarians demands extra patience on the part of the researcher. Materials may have to be presented slowly, taking into account slowed movement and mentation, as well as hearing and visual impairments. Material may also need to be adapted to bypass or overcome sensory deficits. Assessments are often carried out over many visits to avoid tiring the participant. Specific requirements of the participant, such as wearing a hearing aid, use of oxygen, relief of pain before interviewing, and so on, are all important in obtaining good-quality data. Flexibility in scheduling and adapting tasks to the centenarians are crucial for researcher SHCCESS

Psychometric tests may need to be adjusted for centenarians, e.g. large print for reading tests, providing a reading glass, shorter questionnaires, assistance with self-report questionnaires, etc. This is especially important in neuropsychological assessments, as the tests have generally been developed for younger people.

The scoring and interpretation of tests must take age into consideration. Normative data for these tests are generally developed on younger populations, and these may be unsuitable for centenarians. Centenarians may perform poorly on measures on which healthy, younger people perform at a much higher level, thereby putting the centenarians at a disadvantage. Measurement for activities of daily living may be more representative of functional than cognitive ability. Interpretation of the results depends on the concept of 'normality' and the degree of adjustment as acceptable for this age-group.

# Reliance on significant others (informants) for information

Centenarian studies, in particular those that measure cognitive impairment and dementia, often rely on a knowledgeable informant who can provide more objective information. However, the informant may not be very knowledgeable, may suffer from cognitive difficulties, or may have prejudices that compromise the information. It is important to select informants with a certain degree of contact with the participant.

## CONCLUSIONS

The study of centenarians poses special methodological challenges that must be considered in the planning stages of a study. The choice of design depends upon the primary objectives of the study. Biophysical, psychosocial, and ethnographic investigations all have a role in the study of extreme longevity and pose special challenges. As studies on the causes, associations, and consequences of exceptional ageing become more widespread, remaining cognisant of the challenges and limitations will ensure that reliable and informative data emerge.

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