

Methodological issues in the observational studies conducted in older population: a narrative review

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ABSTRACT

Introduction: Well-conducted observational studies may represent valuable tools for getting insight to disease etiology, detecting the effect of age-related changes, and providing an important perspective on health risk factors and disabilities in an aging population. Nevertheless, this kind of research poses several challenges for researchers. The main aim of this narrative review was to address the potential methodological issues in performing the observational studies in the elderly, the factors that influence their participation, and the possible solutions for overcoming the barriers to research in this population.

Methods: Comprehensive search for the papers published in the period from January 1st 1980 until 31st July 2016 in English or Italian was conducted through MEDLINE, Scopus and Web of Science electronic databases. Findings from the included papers were finally summarized.

Results: In cohort studies, the following barriers were addressed: sample size calculation, ascertainment of the target population, frequency of data collection, exposure determination, multifactorial loss to follow-up (drop-outs), cognitive impairment, definition of confounders, and ethical aspects. Case-control studies were reported to be prone to the issues like ascertainment of cases and controls, willingness to participate, data accuracy, recall bias, issues related to patients' multimorbidity, and cognitive impairment.

Conclusions: Important factors to consider in research in elderly people include: precise definition of the study population, well conducted recruitment process, engagement with family and home care staff, cognitive impairment assessment and the consequent relevant ethical and legal issues, relief of participant burden in order to minimize withdrawal, and engagement with the media.

Key words: observational studies, cohort, case control, elderly, older adults

INTRODUCTION

The conduction of epidemiological studies among older adults is a broadly discussed argument since the early 1970s [1]. Considering the limits of experimental designs in geriatric research, well-conducted observational studies might represent the best way of getting insight into disease etiology, the effect of age-related changes, and might provide an important perspective on health risk factors and disabilities in an aging population [2, 3]. Unlike Randomized Clinical Trials (RCT), observational studies assess outcomes of medical intervention in daily and real clinical practice, involving often unselected populations that reflects true compliance with treatment or intervention [4].

In response to the poor generalizability of the RCT's results to the elderly population [5], about 30 years ago, the geriatric research developed the comprehensive geriatric assessment (CGA) [6], a standardized evaluation methodology to perform a global assessment of patients in different care settings. CGA does provide information on various problematic areas of the elderly patient including co-morbidities, syndromes, socio-economic problems, functional and cognitive deficits not covered by the traditional medical assessment. The systematic adoption of CGA instruments for clinical, administrative and/or research purposes, has resulted in more detailed evaluation, improved care planning and guaranteed overall better quality of care. It also contributed to the collection of massive and reliable amounts of information [7]. These high quality clinical databases have been commonly used to conduct observational studies as an alternative methodology to randomized clinical trials in order to address the multifaceted problems of the elderly population in different settings [8, 9].

Although it has been shown that older adults generally agree to participate in research studies, either because they want to improve their social life, or due to the potential study benefits, the practical aspects of research in this population represent a huge challenge [10].

Therefore, the purpose of this narrative review was to summarize the literature evidence on methodological issues in conducting observational studies in the population of older adult, and to address possible solutions to overcome the barriers to research.

METHODS

The comprehensive search was conducted through MEDLINE and Scopus electronic databases. Only the papers focusing on the issue of performing observational studies in elderly subjects, independently of setting, were included. Papers published between January 1st 1980 and 1st July 31st 2016, in English or Italian language, were considered eligible. The combination of the following key words and their synonyms was

used: "elderly" AND "observational study" OR "case-control" OR "cohort study" OR "cross-sectional". The review was conducted screening articles titles, abstracts and ultimately analysing full text articles of potentially eligible papers. The process has been performed in duplicate by two researchers, and disagreements regarding the inclusion of the papers were resolved through consensus. Included articles were also checked for additional references.

Main findings of the included studies and the main issues in conducting observational studies in elderly population and possible suggested solutions to overcome the challenges are presented narratively and synthesized in the tables.

RESULTS

Only few studies have explored the factors that may influence the research in older population, together with the possible solutions for overcoming the possible barriers and challenges. Evidences arising from 19 papers are summarized in Table 1 and 2, respectively for cohort and case-control studies.

The studies enrolling elderly participants are usually prone to the logistical issues related to data collection, definition of the study sample, as well as ascertainment of sufficient and constant participation of older subjects [11].

Some health conditions like hearing problems, that are usually more common in elderly, can impair the communication. This is of particular importance in telephone surveys, and may increase the risk of selection bias. In addition, visual problems can threaten reading and right understanding of the leaflets and the content of study material [12].

Other authors added that besides the abovementioned factors, multi-morbidity and multidrug interaction become highly problematic during the ageing process [13, 14].

More generally, when considering older adults for participation in observational studies, researchers should interpret the symptoms that are more common for older population with caution. Furthermore, they should bare in mind that clinical manifestations of the disease, biomarkers and other measures can greatly differ in this population, as compared to the standard population. Similarly, the differences in clinical outcomes can be explained by the specific ageing physiopathology, lower sensitivity and specificity of serological tests, altered responsiveness to treatments, and higher frequency of secondary adverse clinical outcomes from primary illness. Some additional peculiarities can arise both from intrinsic characteristics of the older adults, such as the age-related cognitive decline that can impede the collection of self-reported information, and from external factors like unusual health care practices related to more intensive and multidisciplinary care [11].

COHORT STUDIES

Longitudinal prospective cohort studies are considered one of the best solutions for investigating the health issues in elderly, especially because of the possibility of getting better insight into disease etiology, detecting the effects of true age changes, and providing an important perspective on health risk factors and disabilities in aging population [2, 3].

However, conducting research in elderly people becomes challenging when the retrospective longitudinal study design is used. As a matter of fact, memory impairment and dementia prevalence, which increase with age, decrease the reliability and validity of data obtained during the interviews [12].

One of the main starting problems in an ageing cohort study is the definition of the target population, in particular the minimum age for establishing the cohort. Nowadays, elderly people (65-years old and older) are generally in better health conditions as compared to previous generations, due to the low rates of disability and health events (i.e. birth-cohort effect) [15]. Therefore, lots of studies have expanded the age study limit to the age of 70 in order to address the problems of aging more comprehensively [3].

Taking into consideration that the majority of health related behaviors occurs earlier in life, the assessment of exposures related to the outcomes of interest, which arise from earlier life periods, can be more complex. In addition, another problem that should not be neglected is the possibility of entering the study without any cognitive or mental issue, and becoming mentally impaired later on [11].

Another important challenge in a prospective ageing cohort is the data collection frequency. Besides the study characteristics, it certainly depends on health, functional and social changes occurring at different rates and intervals, which also differ with age and risk status. Shorter intervals can provide robust information, and at the same time represent a great opportunity to minimize the amount of missing data given the multiple participant contacts. On the other hand, they are more demanding and time consuming for included subjects [11]. Moreover, study costs arise when considering older adult since their unstable health conditions often ask for consecutive measurements of several parameters [12].

Data collection is also influenced by the presence of proxy respondents. When available or appropriate, a relative or a friend can represent a valuable source of information for overcoming physical or cognitive impairment that limits the direct acquisition of the data. The reliability of the information might be limited if the proxy respondent is contemporary of the included subject. For this reason, health care professionals might be an optimal source of information, as pointed out after about 30 years of experience based on the use of the Comprehensive

Geriatric Assessment (GCA)[7]. One of the strengths, especially of the "second and third generation" assessment instruments elaborated by InterRAI, is the standardized training of the health care personnel involved in the data collection process.

It has been ascertained that many health outcomes take many years to occur. Therefore, cohort studies usually require a relevant number of participants, in order to record a sufficient number of events within a predefined follow-up period. This is obviously resource-consuming (i.e. time, money). Thus, appropriate sample size estimation for the primary outcomes of interest represents the crucial step during the study design in order to maximize the likelihood of detecting the events of interest [11].

All longitudinal studies are prone to multifactorial attrition, mainly due to the losses to follow-up, decline in study participation rates and non-response, but these issues are particularly noticeable in the ageing studies where the number of drop-outs tends to grow as age advances. This is surely one of the biggest concerns, because it can cause low representativeness of the sample and significantly impact the assessed outcomes and statistical efficacy [16]. For example, an incidence analysis can be significantly altered by the the loss of the cases, which becomes even more evident when the study is focused on rare health conditions [16]. The attrition is directly associated with the follow-up period; the longer it is the higher is the possibility for drop-out [16]. Similarly, the older is the cohort, the higher are the non-participation rate and drop-outs [11]. According to the several group of authors, attrition is associated with age, lower educational levels, poor functioning and cognitive impairment, living alone and being single [16,17]. Attrition rates showed wide variability across different settings, such as in the case of studies carried out on patients with cognitive decline, where dropouts range from 30% to 95% of the enrolled patients [18,19].

Additionally, longitudinal studies in older adults may be prone to increases in costs and burden due to some potential confounders such as education, age and smoking history. [3]. As a matter of fact, age in this kind of studies is both a key variable, and a potential confounder. Additionally, some other potential confounders, such as depression, impaired cognitive status and lacking social support need to be assessed, since they are of particular interest in the older adult population [3].

Many useful statistical modeling approaches for longitudinal data are available to address the possible confounders and include the following models: Cox proportional hazards models, extended Cox multistate transition models, generalized estimating equations, generalized linear models, and joint modeling methods [20].

Some ethical aspects should also be considered when approaching to the elderly population. Personal interviews and physiological measures require an informed consent which can be more difficult to obtain from an

elderly person, due to sensory or cognitive impairments, or sometimes also due to the lack of needed privacy [12]. Obtaining an informed consent from older adults is of extreme importance, particularly in those disabled by stroke, affected by Parkinson’s disease or institutionalized, and therefore poses a great ethical challenge [21]

Strategies to minimize drop-outs and to encourage the participation of elderly in longitudinal studies may include providing additional information with newsletters, feedback about the study, personal response to queries, meetings, easily accessible study website, birthday cards and letters from the Principal Investigator. Other possible solutions for increasing the compliance to the study can comprise greater involvement of media, provision of small gifts or symbolic amounts of money, a special attention to practical issues such as transportation to the medical centers or home visits organization [16].

In the study by Davies et al. the response rate increased using the named photographs of the nurses involved in the research process, together with the information booklet for the Newcastle 85+ Study. The strategy showed the effectiveness that was followed by the participants’ positive feedback on this action [22]. Similarly, other groups of authors reported that direct telephone contact with older participants or home visit following the initial invitation letter seemed to be even more useful for increasing the patients’ interest to participate to the study [23-25].

CASE-CONTROL STUDIES

Case-control studies are used to investigate and obtain, in relatively short time and at reasonably low cost, reliable information about causative factors also concerning rare diseases. This type of study conducted in the population of older adults has many methodological and logistical issues in common with cohort studies. However, some of them remain specific for this study design [11, 13].

Firstly, some health conditions may change through the lifetime and be biologically different as compared to the “same” condition diagnosed earlier. Therefore,

a clear definition of the case is mandatory, especially when assessing conditions that differ in stages of severity. Several pathological pathways may be altered by previous lifestyles (i.e. weight, smoking, diet or use of substances), as well as numerous infectious and chronic diseases that occurred earlier in life may influence the disease manifestation.

The ascertainment of older cases and controls is impeded by several factors: living in residential homes or institutions may decrease the possibility for the recruitment, given the fact that some of the patients can be protected from contact with the investigators by family members or other persons (“gate-keeping” role). Willingness of the older persons to participate as cases or controls is further influenced by multi-morbidity and age-related cognitive dysfunction. Moreover, logistic problems such as lack of transportation or the long distance to the place where the study is performed may impede the participation, and this requires a careful consideration of the proxy respondents’ involvement [11].

Since cognitive impairment, as one of the most common health issues in elderly, may decrease the quality of the interview, the data collection represents a critical step. The recall bias in elderly emerges as a major problem in all case-control studies, considering that most of them are not conducted using clinical, employment or environmental records. Memory support, such as timeline techniques and, when available, proxy respondents can improve the data accuracy.

When approaching this study design, the correct matching of cases and controls is a basic epidemiological technique that should be performed in order to reduce bias. Older adults’ multi-morbidity exponentially increases the number of potential variables to consider, making the matching a particularly complex and delicate issue [11].

CROSS-SECTIONAL STUDIES

Another type of observational design, cross-sectional study, is characterized by lack of precise description of the disease course in the older persons. This may be due

TABLE 1. Main issues in conducting cohort studies in elderly population and solutions to overcome the challenges.

Issues	Possible solutions
<ul style="list-style-type: none"> • Sample size calculation • Ascertainment of the target population • Frequency of data collection (intervals between waves) • Exposure determination • Multifactorial loss to follow-up (drop outs) • Multimorbidity • Cognitive impairment • Definition of the potential confounders • Ethical aspect 	<ul style="list-style-type: none"> • Expansion of the age study limit • Provision of additional information (i.e newsletters, feedback on the study, personal response to queries, meetings, etc). • Card providing the date, time and length of the next visit • Involvement of media, small gifts or symbolic amounts of money, transportation to medical centers or offering home visits. • Direct telephone contact or home visit following the initial invitation letter • Proxy respondents • Inclusion in the analysis of the possible confounders • Use of modeling methods

TABLE 2. Main issues in conducting case-control studies in elderly population and solutions to overcome the challenges.

Issues	Possible solutions
<ul style="list-style-type: none"> • Ascertainment of cases and controls • Willingness to participate • Data accuracy (Recall bias, Bias due to confounding) • Multimorbidity, Cognitive impairment 	<ul style="list-style-type: none"> • Memory support (timeline techniques) • Proxy respondents • Matching the cases and controls • Help of specifically trained professionals

to the different factors that regulate their health state such as age changes, pathological conditions, as well as some determinants of social and environmental influences (pseudo-ageing) [1].

Even if cross-sectional studies will not be detailed in this paper, it might be useful to remind that they represent an important source of exploratory and hypothesis-generating results. The above-mentioned CGA has been widely used for transversal study, especially throughout record-linkage techniques. For example, the SAGE dataset (containing data on residents of 1492 nursing homes of 5 U.S. states assessed with MDS-NH instruments) has been linked with the Centers for Medicare and Medicaid claims files, the semi-annual survey done for certification purposes and the Area Resource File, enabling the exploration of several clinical questions like falls, pain, prevalent medical conditions like hypertension, dementia, cardiovascular conditions and diabetes. Results based on analyses of the SAGE database have provided guidance to develop programs to improve appropriate prescription (i.e., analgesics) and to reduce the use of inappropriate medications [26].

CONCLUSIONS

This review addresses the main challenges that researchers are facing when conducting studies involving aging population, especially in the context of observational studies. Furthermore, it provides insight into some of the possible solutions to overcome these issues on their pathway.

Retention (maintenance of constant participation) of persons with reduced cognitive abilities is challenging and multimorbidity represent an important aspect to bare in mind in study outcome design and measure assessment.

Important factors to consider when engaging older participants in research include: precise definition of the study population, well conducted recruitment process, engagement with family and home care staff who interacts with older adults, cognitive impairment assessment (with the consequent relevant ethical and legal issues), relief of participant burden in order to minimize withdrawal, and engagement with the media.

Still, observational studies remain simpler research design respect to the more complex randomized clinical trials which require significant time, resources, and

infrastructure to be completed, and may be conducted in a more cost-effective and timely way than RCTs [27].

Therefore, in order to guarantee that the future care provided to our ageing populations will be based on the best quality evidence, it is imperative to pursue well-designed observational studies, with satisfying participation rates, assuring the reliability and validity of collected data.



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