

SYSTEMATIC REVIEW

Analysis of recurrent events: a systematic review of randomised controlled trials of interventions to prevent falls

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Abstract

Rationale: there are several well-developed statistical methods for analysing recurrent events. Although there are guidelines for reporting the design and methodology of randomised controlled trials (RCTs), analysis guidelines do not exist to guide the analysis for RCTs with recurrent events. Application of statistical methods that do not account for recurrent events may provide erroneous results when used to test the efficacy of an intervention. It is unknown what proportion of RCTs of falls prevention studies have utilised statistical methods that incorporate recurrent events.

Methods: we conducted a systematic review of RCTs of interventions to prevent falls in community-dwelling older persons. We searched Medline from 1994 to November 2006. We determined the proportion of studies that reported using three statistical methods appropriate for the analysis of recurrent events (negative binomial regression, Andersen–Gill extension of the Cox model and the WLW marginal model).

Results: fewer than one-third of 83 papers that reported falls as an outcome utilised any appropriate statistical method (negative binomial regression, Andersen–Gill extension of the Cox model and Cox marginal model) to analyse recurrent events and fewer than 15% utilised graphical methods to represent falls data.

Conclusion: RCTs that have a recurrent event end-point should include an analysis appropriate for recurrent event data such as negative binomial regression, Andersen–Gill extension of the Cox model and/or the WLW marginal model. We recommend that researchers and clinicians seek consultation with a statistician with expertise in recurrent event methodology.

Keywords: recurrent events, falls, elderly

Introduction

Evidence-based medicine has been promoted by the use of standards for reporting the design and methodology of randomised controlled trials (RCTs). An ever-increasing number of journals require that authors adhere to the Consolidated Standards for Reporting Trials (CONSORT) statement when

reporting clinical trials [1]. The aim of that statement is to improve the consistency of data presentation so that readers can better assess the strengths and limitations of an RCT. To date, there are no guidelines for reporting events where the outcome can occur recurrently (e.g. falls, fractures, certain cancers and infections, chronic disease exacerbations).

To date, RCTs of falls prevention strategies most commonly report the time to first event and the proportion of

Table 1. Search strategy and number of papers retained at each stage

Search stage	Papers retained
Medline search strategy	
1. Clinical trial.pt. or random.mp. or randomized controlled trial.mp. or Randomized controlled trial.pt.	7,313,389
2. Exp accidental falls/	7,453
3. (Falls or faller\$).tw.	16,014
4. 2 or 3	19,972
5. Exp aged/	1,646,570
6. (Older or senior\$ or elderly).tw.	241,395
7. 5 or 6	1,735,285
8. 1 and 4 and 7	1,076
9. Limit 8 to English language	1000
10. Limit 8 to yr = '1994-2006'	893
Assessment based on title and abstract	113
Assessment based on reading entire paper	77 ^a

Note: Six additional studies were identified by reference checks; therefore, 83 studies were included.

participants who experience a fall. If only the time to first event is reported, as in Cox proportional hazard survival analysis, the study may conclude that the treatment is ineffective when the intervention may influence recurrence of the events 2, 3 and so on (see [2] for an example). Comparing only the proportion of participants who experience a fall within a time period is analogous to a time to first event analysis. Also, comparing proportion of participants who experience a fall discards valuable prospectively collected falls data in participants with unequal follow-up. The Prevention of Falls Network Europe (ProFaNE) has developed a common outcome data set for fall injury prevention trials [3]. These guidelines and a recent systematic review of definitions and methods of measuring falls in RCTs [4] suggest that trials report the rate of falls. However, at present there are no papers outlining specific statistical methods for analysing recurrent events such as falls.

Because of the lack of a definitive paper on how to analyse and report recurrent events such as falls, we systematically reviewed the statistical methods used in falls prevention RCTs to determine whether the proportion of RCTs using appropriate methods has increased from the period 1994–99 to 2000–06.

Methods

We searched Medline for articles published between 1994 (the first successful RCT to prevent falls in community-dwelling older adults was published [5]) and November 2006 inclusive. The search query consisted of a Boolean combination of relevant text words and database subject headings describing falls prevention in community-dwelling older persons (Table 1). The elements of the search query used to identify RCTs have been previously published [6]. We included all English language articles published in peer-reviewed journals that were RCTs in community-dwelling

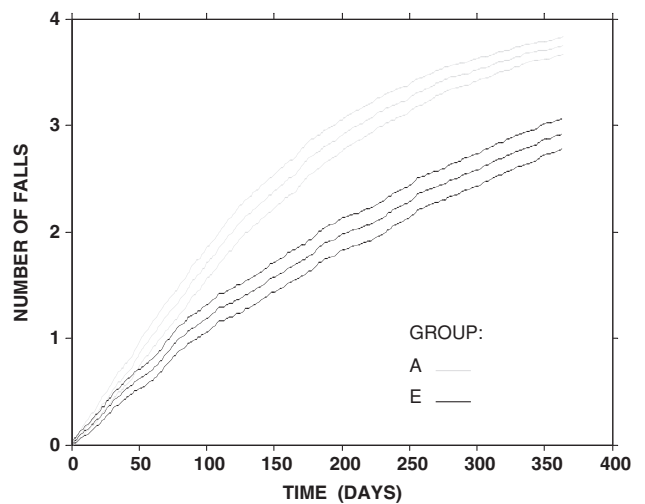


Figure 1. Assessment of studies for inclusion in RCTs of recurrent events.

persons aged 60 years and older that reported falls as an outcome. We included articles that reported individual level meta-analyses. We also included articles that reported secondary analyses of a previously published trial. No assessment of quality was undertaken for each included trial.

The search strategy was validated against 10 authoritative articles in the field which were identified a priori [5, 7–15]. Included articles were also compared to references from two recent systematic reviews of falls prevention to assess sensitivity of our search strategy [16, 17].

We screened the title and abstract of the selected articles for the inclusion criteria and the full articles were retrieved if relevant. These articles were assessed independently by two of the authors (M.G.D. and B.S.).

We developed a data abstraction form based on previous literature to standardise the description of methods for each study [18–20]. It included study duration, number of dropouts due to death, duration of follow-up time, method of falls ascertainment, graphs and statistical methods with graphical display (23) and inferential statistics (3).

The reviewers independently read each article and completed the checklist related to statistical methods (19 items) (M.G.D. and B.S.). The checklists for both reviewers were compared for each article and discrepancies were resolved by consensus.

We report the prevalence of statistical methods using recurrent events by proportion of all articles. We compared the prevalence of these methods between two publication intervals, 1994–99 and 2000–06 using the chi-square statistic.

Results

The flow of trials through the systematic review is displayed (Figure 1). Of the 83 articles included, 77 (93%) were identified by the Medline search and the remaining articles were identified by the reference lists from two recent systematic reviews. Among the included articles, two were

Table 2. Statistical methods with graphical display and number of papers (proportion) by publication year

	Number of papers (%)	
	1994–99 <i>n</i> = 23	2000–06 <i>n</i> = 60
Graphical display and method used		
.....		
Kaplan–Meier-based approaches		
Time to first fall	3 (13)	5 (8)
Mean cumulative function-based approaches	0 (0)	0 (0)
Bar charts or pie charts		
Proportion of patients with stated number of falls	0 (0)	4 (7)
Mean number of falls	0 (0)	0 (0)
Other	0 (0)	5 (8)
No graphical presentation of falls data	20 (87)	46 (77)

Note: Columns do not sum up to the total number of papers as studies might have used more than one method to analyse falls.

individual-level meta-analyses (see references 61 and 63); references 57 and 71 report results from the same trial and reference 10 is a 2-year follow-up of reference 11. Reference 64 is a re-analysis of references 11 and 65. There were six cluster RCTs (references 16, 39, 44, 71, 74 and 83; see Appendix 1 available on *Age and Ageing* online for the references cited in this paragraph).

The proportion of articles in the two publication intervals, 1994–99 and 2000–06, was 28% (23/83) and 72% (60/83), respectively. The studies included were published predominantly in geriatrics and ageing journals (54%, 45/83) and general medical journals (22%, 18/83). The studies included between 18 and 5,292 participants (mean 504, median 236) and reported an observation period between 5 and 260 weeks (mean 55, median 52). Nearly all studies (92%, 76/83) reported variable participant follow-up times and lost between 0 and 17% of participants due to death. The methods for ascertaining falls in the 83 studies were monthly diary (33%, 27/83), recall at the final follow-up (34%, 28/83), weekly diary (7%, 6/83), monthly telephone call by the investigator (6%, 5/83) and weekly telephone call by the investigator (1%, 1/83). The method of ascertaining falls was not reported in 6 of the 83 studies.

All 10 of the ‘key’ articles identified a priori by the investigators were retrieved by the search. The rate of agreement on analysis method was 91% for specified statistical methods. Discrepancies were resolved by consensus.

The prevalence of the statistical methods with a graphical display by year of publication is shown in Table 2. The most prevalent statistical method with a graphical display was the Kaplan–Meier method (8/83) where authors estimated the cumulative probability of surviving and remaining free of a fall over the follow-up time. None of the articles included in this study used the mean cumulative function to display the average number of falls per participant by a certain time. We did not observe an increase in the proportion of articles utilising graphical displays to depict recurrent events from 1994–99 to 2000–06.

Table 3. Inferential statistics and number of papers (proportion) by publication year

	Number of papers (%)	
	1994–99 <i>n</i> = 23	2000–06 <i>n</i> = 60
Inferential statistics used		
.....		
Log-rank/proportional hazards-type approaches		
Time to first fall	7 (30)	11 (18)
Proportions/odds ratio-based approaches		
Proportion with any falls	13 (57)	34 (57)
Proportion with two or more falls	4 (17)	11 (18)
Normal error approaches (e.g. <i>t</i> -tests, linear regression, ANOVA)		
Number of falls	2 (9)	15 (25)
Non-parametric approaches (e.g. Mann–Whitney <i>U</i> -test)		
Number of falls	4 (17)	7 (12)
Average rate of all events		
Relative risk based approaches	9 (39)	26 (43)
Methods appropriate for recurrent events		
Negative binomial regression model	4 (17)	16 (27)
Andersen–Gill model	4 (17)	2 (3)*
WLW marginal model	0 (0)	3 (5)
Other	1 (4)	3 (5)
No inferential statistics for falls	3 (13)	1 (2)
Unclear what analysis has been used	2 (9)	1 (2)

* χ^2 , $P = 0.03$, all remaining comparisons were not statistically significant.

Note: Columns do not sum up to the total number of papers as studies might have used more than one method to analyse falls.

Table 3 details the prevalence of the inferential statistical methods by year of publication. The most prevalent inferential statistical method reported was proportion of participants having at least one fall (47/83, 57%). Less than one-third of the articles reported at least one of the three recurrent event statistical methods (26/83). The prevalence of the negative binomial regression model, Andersen–Gill model and WLW marginal model was 25, 7 and 4%, respectively. There was no significant increase in the proportion of articles reporting negative binomial regression and marginal models. The proportion of articles reporting the Andersen–Gill model was significantly less in the period 2000–06 compared to 1994–99 (χ^2 , $P = 0.03$).

Discussion

These findings suggest that in falls-related RCTs, the three well-established statistical methods for repeated events—negative binomial regression model, Andersen–Gill model and WLW marginal model—are under-used. As these methods have not been used consistently, the validity of these studies diminishes. Although the purpose of this systematic review was not to directly compare the results from these three methods using either simulation studies or existing data, the comparison of these methods and other methods for recurrent events has been published elsewhere [18, 21].

Recurrent events are the primary outcomes in many clinical scenarios and not just falls. They are relevant to many conditions of aging such as hospitalisations, fractures and upper respiratory tract infections. There has been a considerable debate as to analysis methods for recurrent events. On the one hand, it was suggested that simply reporting the events per person-year and ignoring the dependence of multiple events within participants is seriously flawed and investigators should report only the first event, using both proportion and time to event analysis [22]. On the other hand, authors have argued for reporting the rate of recurrent events to avoid incorrect conclusions by ignoring valuable information such as when the intervention fails to impact the first event but nevertheless influences subsequent events [2]. This is illustrated in an RCT of expedited cataract surgery to prevent falls conducted by Harwood and colleagues [23]. There was no significant difference between groups using time to first fall; however, when the rate of falls was compared, the rate of falls was 33% lower in the intervention group compared to the control group. Furthermore, sample size can potentially be reduced when all events are considered in the analysis compared with time to first event analysis [24]. However, these calculations are not straightforward and factors such as subject accrual, duration of follow-up, event rate parameters and dropout rates must be considered (please see Appendix 2 for further details, available on *Age and Ageing* online).

The mean cumulative function provides the average cumulative number of events per subject over time and the corresponding 95% confidence interval [25–27]. The MCF can be plotted, and the graphs allow for an easy interpretation of the average number of events expected in one participant at a certain time. It can also illustrate (i) when interventions begin to take effect (where the curves for the intervention and control group begin to diverge) and (ii) determine on average how many events are prevented per participant by a certain time (the difference between the two curves at any given time). Finally, the mean cumulative function graph may illustrate how intervention and control groups behave over time. For example, these graphs may help to determine when an intervention is flagging (for whatever reason) and may prompt a reassessment and initiate changes to the intervention program (e.g. compliance may be a problem). Please see Appendix 2 for more details and an example of the MCF curves (available on *Age and Ageing* online).

To our knowledge, this is the first systematic review in the falls literature to evaluate the prevalence of statistical methods. We searched Medline and used the references from two recent systematic reviews to obtain 83 articles; although we may have missed articles, it is likely that we missed both articles that did and did not utilise the three appropriate statistical methods. We recognise that the three methods discussed in detail do not cover all the options (e.g., semiparametric method developed by Lin and colleagues [28]), nor do we address other complex analysis issues that arise in the analysis of recurrent events. We direct the reader to other literature that addresses fine statistical details further [20, 24, 26, 29–31].

Although we contend that our findings have relevance to clinical conditions where outcomes occur recurrently, this study only included RCTs that reported falls. Notably, a recent systematic review of hospitalisations suggests that the appropriate statistical methods are also under-utilised [19]. Therefore, we recommend that clinicians and researchers consult with statisticians with expertise in the area of recurrent event analysis to help choose an appropriate statistical model that will answer the study question.

Key points

- Falls is a major public health problem that occurs repeatedly in seniors.
- There are several accepted and available statistical methods to analyse recurrent events such as falls including negative binomial regression, Andersen–Gill extension of the Cox model and marginal Cox regression models. Other methods such as time to first fall and proportion of fallers are analysis methods that can provide erroneous results when used to test the efficacy of an intervention that may affect subsequent events.
- Our systematic review suggests that fewer than one-third of 83 papers that reported falls as an outcome utilised an appropriate statistical method to analyse recurrent events.
- Our data suggest the need for guiding bodies such as CONSORT to include analysis standards for RCTs that have a recurrent event end-point.

Conflicts of interest

There are no conflicts of interest.

Supplementary data

Supplementary data are available at *Age and Ageing* online.

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