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Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations

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Abstract

Objectives: To describe the use and reporting of interrupted time series methods in drug utilization research.

Study Design and Setting: We completed a systematic search of MEDLINE, Web of Science, and reference lists to identify English language articles through to December 2013 that used interrupted time series methods in drug utilization research. We tabulated the number of studies by publication year and summarized methodological detail.

Results: We identified 220 eligible empirical applications since 1984. Only 17 (8%) were published before 2000, and 90 (41%) were published since 2010. Segmented regression was the most commonly applied interrupted time series method (67%). Most studies assessed drug policy changes (51%, $n = 112$); 22% ($n = 48$) examined the impact of new evidence, 18% ($n = 39$) examined safety advisories, and 16% ($n = 35$) examined quality improvement interventions. Autocorrelation was considered in 66% of studies, 31% reported adjusting for seasonality, and 15% accounted for nonstationarity.

Conclusion: Use of interrupted time series methods in drug utilization research has increased, particularly in recent years. Despite methodological recommendations, there is large variation in reporting of analytic methods. Developing methodological and reporting standards for interrupted time series analysis is important to improve its application in drug utilization research, and we provide recommendations for consideration.

Keywords: ARIMA; Drug utilization; Pharmacoepidemiology; Review; Segmented regression; Time series

1. Introduction

Interrupted time series analysis is the strongest and most commonly used quasi-experimental design to assess the impact of an intervention when a randomized controlled trial is not feasible [1–6]. This method has been applied in a variety of disciplines and was first introduced to the field of health services research in 1981 to evaluate the impact of regionalized perinatal care [7]. Interrupted time series methods use aggregate data collected over equally spaced intervals before and after an intervention, with the key assumption that data trends before the intervention can be extrapolated to predict trends had the intervention not occurred [3]. Routinely maintained pharmacy and medical databases provide rich data sources to apply interrupted time series methods [3].

Several methodological issues need to be considered when completing an interrupted time series analysis. First,

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What is new?

- There has been an increase in the application of interrupted time series analysis in drug utilization research, particularly in recent years.
- We identified large variation in methodological considerations reported in empirical applications.
- Developing methodological and reporting standards for interrupted time series analysis is important to improve its application in drug utilization research, and we provide recommendations for consideration.

given the serial nature of the design, autocorrelation, nonstationarity, and seasonality need to be considered [3,8]. Autocorrelation refers to the serial dependence of outcome measure error terms. For example, prescription patterns closer to each other may be more similar than those further apart [3,5,6]. The presence of autocorrelation can be assessed using the Ljung–Box chi-square statistic [9] or Durbin–Watson statistic [3,5,6,10] and corrected for if necessary. Nonstationary data exhibit an underlying trend that is unrelated to the intervention. For example, the use of a drug commonly increases once it enters the market [8]. Nonstationary can be tested using the augmented Dickey–Fuller test [11]. Seasonality represents regular seasonal fluctuations in the outcome, for example, use of medications to treat influenza. When present, terms for seasonality (e.g., months) should be included in the model [3,6]. Failing to account for autocorrelation, nonstationarity, and seasonality may lead to biased results.

The number of data points available for analysis and the number of observations within each data point are important when using interrupted time series analysis. Although there is no gold standard, it is generally agreed that more data points and observations are better. Depending on the minimum effect size and the amount of variation, a minimum of nine data points preintervention, postintervention, and when applicable, between interventions [4,12], and at least 100 observations per data point is encouraged [3]. A larger number of observations in each data point provides more stable estimates and thus reduces the variability and outliers within a time series analysis. Data point outliers that are explainable, such as a sudden peak in drug dispensing in anticipation of a drug restriction policy, can be controlled for using an indicator term [3]. Outliers that result from random variation can be treated as regular data points [3]. A larger number of data points also permit more stable estimates for forecasting preintervention trends had the intervention not occurred. In general, however, caution should be used when forecasting beyond the data points observed in interrupted time series analyses. Another caveat when conducting interrupted time series analysis relates to possible outcome measure ceiling or floor effects. For example, when studying the impact of an intervention in improving the proportion of patients treated with a drug, the outcome has a natural ceiling of 100%, and thus, depending on the initial level of measurement, minimal change in the outcome may be observed [13]. Authors must consider ceiling and floor effects when designing their study and interpreting results.

A clear intervention time point helps to identify preintervention and postintervention data points, yet if intervention effects are gradual or delayed, then a lag period may be considered [3]. Lagged intervention effects can be accounted for by excluding the lag period from the analysis, modeling the lag period as a separate segment in the time series [3], or using a ramp function in autoregressive integrated moving average (ARIMA) models [14]. Here, graphical figures displaying the results of interrupted time series analysis are particularly useful. Even without statistical output, figures allow readers to visually examine baseline trends, the time point at which the intervention occurred, and the impact of the intervention [3,5]. All interrupted time series studies should therefore include graphical display to facilitate interpretation of study results.

The main threat to validity in interrupted time series analysis relates to time-varying confounding, such as changes in outcome coding, cointerventions, or changes in the population under study [3–5,15]. These threats need to be considered at the individual study level and require intimate knowledge of the data and health care utilization trends. The use of a comparison outcome in the same population, or a comparison group using the same outcome in a group not exposed to the intervention, helps to alleviate concerns related to time-varying confounding [3,5]. Indeed, an advantage of interrupted time series analysis is the ease in stratifying results by different groups [5].

Interrupted time series analysis has been applied in a variety of disciplines; however, its use to study the impact of health care interventions on drug utilization has not been well described. The purpose of our study was to describe the use and reporting of interrupted time series methods in drug utilization research.

2. Methods

We completed a systematic MEDLINE keyword and Web of Science citation search to identify all English language articles that used interrupted time series methods to study drug utilization in humans. Empirical applications that examined the impact of interventions at the population level, including drug policy changes, new evidence in the form of guideline changes or major publications, quality improvement interventions, and government or media safety advisories; on prescription drug utilization were eligible. We defined drug utilization as the number or proportion of

drug(s) dispensed, patients dispensed a drug, or patients meeting an adherence target. Systematic reviews, methodological contributions, letters to the editor, and conference abstracts were excluded because the focus was on use and reporting of empirical applications. We also excluded single institution studies so we could focus on population-based interventions that may be more generalizable.

We first searched MEDLINE from inception (1946) to December 2013 with keyword terms related to time series analysis and drug utilization (Appendix A at www.jclinepi.com). We then used Web of Science to perform a citation search of methodological articles identified in the keyword search [3,5,16] and a commonly cited article [7]. Finally, we manually searched reference lists from all methodological contributions [B.1–10, Appendix B at www.jclinepi.com], review articles [B.11–14], and eligible empirical applications [B.15–203] identified in the keyword and citation searches to identify additional empirical applications. Two authors (R.J. and A.M.B.) independently completed each search and reviewed articles for eligibility. Discrepancies were resolved through discussion with a third author (S.M.C.). A proportional Venn diagram was created to illustrate the number of empirical applications identified by each search strategy. The number of empirical applications was then plotted by publication year.

We abstracted the following characteristics for each application: intervention(s) of interest, primary data source, and methodological detail (time intervals, outcome measure, interrupted time series methods used, and methodological considerations reported). As previously described, there are several methodological considerations in interrupted time series analysis, and we have taken care to abstract whether authors reported these; however, we were unable to evaluate aspects that would require access to each study's raw data. Thus, methodological considerations abstracted included reporting of autocorrelation, nonstationarity, and seasonality; use of a comparison group; clearly defined time points; number of preintervention and postintervention points; outliers; forecasting; and absolute and/or relative changes with confidence intervals or standard errors. Additional considerations abstracted included the use of lag periods, sensitivity analysis, and graphical figures to display results. One author (R.J.) abstracted all data, and a second author (A.M.B.) verified all abstracted data. All methodological considerations were summarized using descriptive statistics.

3. Results

Of 1917 unique articles identified, 10 were methodological contributions [B.1–10], 4 were review articles [B.11–14], and 220 were eligible empirical applications [B.15–234] (Fig. 1, Appendix B at www.jclinepi.com).

Each search strategy proved important, with 52 empirical applications (24%) identified solely by the keyword search, 33 (15%) identified solely by the citation search, 30 (14%) identified solely by the reference list search, and only 35 (16%) identified by all three search strategies (Fig. 2). Most segmented regression articles (92 of 134, 69%) were identified by the citation search, whereas most ARIMA articles (26 of 31, 84%) were identified by the keyword search. One eligible article that did not appear

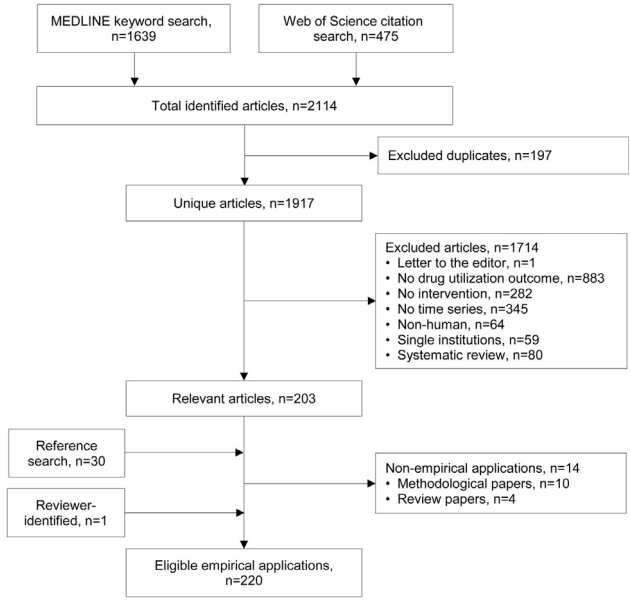

Fig. 1. Flow diagram of systematic search results. MEDLINE was used for the keyword search using search terms (Appendix A at www.jclinepi.com), and Web of Science was used for the citation search [3,5,7,16].

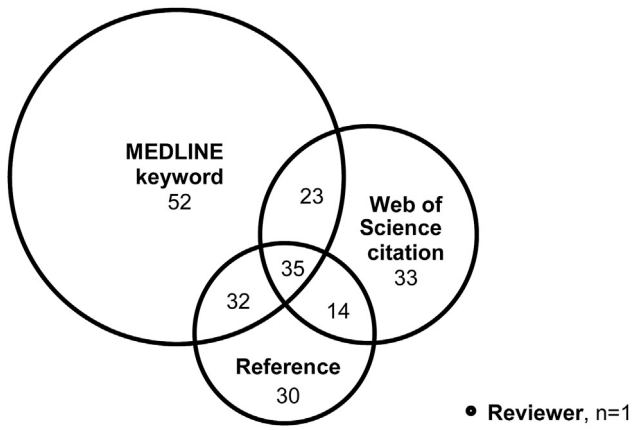

Fig. 2. Proportional Venn diagram of search result yield of empirical applications by search strategy, $n = 220$. The size of each circle is proportional to the relative number of articles identified. MEDLINE keyword search terms are listed in Appendix A at www.jclinepi.com, and four articles were used in the Web of Science citation search [3,5,7,16]. The reference search included all eligible empirical applications ($n = 189$), methods ($n = 10$), and reviews ($n = 4$) identified by the keyword and citation searches. One article not indexed in MEDLINE or Web of Science databases was identified by a reviewer during the peer-review process [B.212].

in our original search was identified by a reviewer during the peer-review process [B.212].

The first empirical application was published in 1984, yet relatively few (n = 17, 8%) were published before the year 2000 (Fig. 3). Since 2000, use has increased with an average of 15 (standard deviation = 8.2) applications published per year. Forty-one percent (n = 90) were published in the last 4 years, with a high of 31 articles published in 2013.

Table 1 summarizes the characteristics of the 220 empirical applications identified, of which 92% used administrative pharmacy databases. Drug policy changes were the most common interventions evaluated (51%), followed by new evidence (22%), safety advisories (18%), and quality improvement interventions (16%). Seventy-one percent examined prescriptions dispensed (22% number, 35%, proportion, and 14% standard dose) as the primary outcome measure, and 29% used the number or proportion of patients dispensed the drug of interest or meeting an adherence target. Most applications examined drug utilization over monthly (76%) or quarterly (14%) intervals. Of the 200 articles (91%) reporting detailed methods, segmented regression (67%), ARIMA models (16%), and linear regression (11%) were the most commonly applied analyses. Other analytical methods included generalized estimating equations, logistic, nonlinear, and Poisson models. Fifty percent (n = 67) of articles using segmented regression applied a linear model.

Of all empirical studies, 146 (66%) reported testing for autocorrelation (77% of ARIMA articles and 73% of segmented regression articles), 68 (31%) reported adjusting for seasonality (52% of ARIMA and 29% of segmented regression), and 32 (15%) reported testing for nonstationarity (65% of ARIMA and 9% of segmented regression). One-third (35%) of all empirical studies reported the use of a comparison group, 70% reported absolute and/or relative impacts with confidence intervals or standard errors, and 28% reported including lag periods in their models. Most articles (85%) clearly reported the intervention time point(s) of interest, and 84% of studies included a graph,

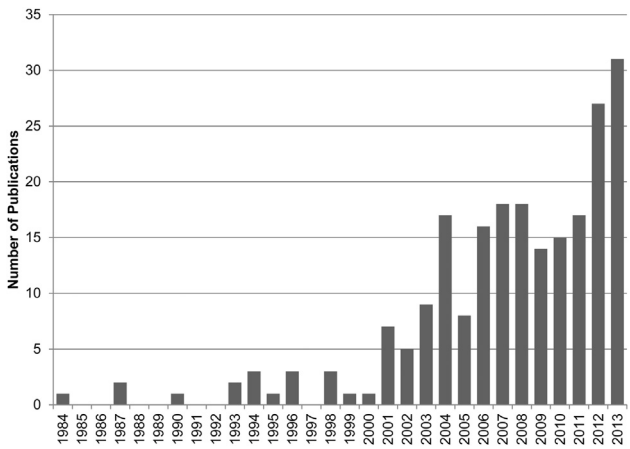

Fig. 3. Number of interrupted time series empirical applications in drug utilization research, by publication year, n = 220.

Table 1. Characteristics of interrupted time series applications in drug utilization, n = 220[a]

Characteristic	n	%
Intervention		
Drug policy changes	112	50.9
Copayments or cost sharing	33	15.0
New drug or drug withdrawal	15	6.8
Prior authorization	21	9.5
Reimbursement changes	43	19.5
New evidence	48	21.8
Guideline changes	15	6.8
Major publications	33	15.0
Quality improvement interventions	35	15.9
Educational	18	8.2
Other quality improvement	17	7.7
Safety advisories	39	17.7
Data source		
Administrative data	203	92.3
Medical charts	10	4.5
Survey data	7	3.2
Time point intervals		
Monthly	166	75.5
Quarterly	31	14.1
Other (e.g., annually, biannually, biweekly, weekly)	23	10.5
Primary outcome measure		
Patient	64	29.1
Number	15	6.8
Proportion	49	22.3
Prescriptions	157	71.4
Number	49	22.3
Proportion	77	35.0
Standardized dose (e.g., daily defined dose)	31	14.1
Interrupted time series method reported[b]	200	90.9
ARIMA models	31	15.5
Reported intervention function (e.g., point, ramp, step)[c]	18	58.1
Linear regression	22	11.0
Segmented regression	134	67.0
Linear models[d]	67	50.0
Other models[d] (e.g., GEE, logistic, nonlinear)	9	6.7
Not specified[d]	58	43.3
Other regression (e.g., GEE, logistic, nonlinear, Poisson)	14	7.0
Statistical considerations reported		
Autocorrelation	146	66.4
Comparison group	77	35.0
Confidence intervals or standard errors reported with estimates	153	69.5
Forecasting using preintervention trends	64	29.1
Graphical figures to display results	184	83.6
Lag periods	61	27.7
Nonstationarity	32	14.5
Number of preintervention and postintervention data points	86	39.1
Outliers	17	7.7
Seasonality	68	30.9
Sensitivity analysis	45	20.5
Time point clearly defined	186	84.5

Abbreviations: ARIMA, autoregressive integrated moving average; GEE, generalized estimating equation.

[a] Some characteristics are not mutually exclusive, thus proportions add to greater than 100%.

[b] For articles reporting detailed time series methods only, n = 200.

[c] For articles reporting ARIMA only, n = 31.

[d] For articles conducting segmented regression only, n = 134.

yet only 39% reported the number of preintervention and postintervention data points included in their analysis (range 3–72 data points). One-fifth (21%) of applications conducted a sensitivity analysis.

4. Discussion

We examined the application and reporting of interrupted time series analysis methods in drug utilization research. Use of interrupted time series analysis has increased since the year 2000, a finding noted in other recent reviews of innovative methods in pharmacoepidemiology [17,18]. The most common interrupted time series methods were segmented regression (67%), ARIMA models (16%), and linear regression (11%). When executing time series models, several methodological aspects are important and may impact the validity of the model. We identified that most eligible articles using ARIMA models addressed autocorrelation (77%), nonstationarity (65%), and seasonality (52%). Because ARIMA models inherently account for autocorrelation, nonstationarity, and seasonality [19], it is possible that authors may have chosen not to report these considerations. In contrast, segmented regression models do not intrinsically account for autocorrelation, nonstationarity, and seasonality, and thus, it is imperative to consider each [3]. However, only 73% of segmented regression studies reported testing for autocorrelation, 29% reported adjustment for seasonality, and only 9% reported consideration of nonstationarity.

Over 80% of interrupted time series analyses cited a clearly defined intervention time point and used figures to graphically display results; however, other methodological issues were poorly reported. Explicit reporting of all methodological considerations may improve awareness of their importance and the interpretation of interrupted time series studies. Therefore, based on prior suggestions [3–6,12,20], we recommend the following be reported in all interrupted time series applications: (1) autocorrelation, nonstationarity, and seasonality considerations; (2) intervention time point(s) and lag periods; (3) the number of data points preintervention, postintervention, and between intervention(s); (4) specific statistical regression methods and the appropriateness of a linear model when applied; and (5) absolute and/or relative changes from baseline (intervention impact) with significance. We also recommend that all interrupted time series studies: (1) use a graphical display with clearly defined time point(s) to present results; (2) comment on: the minimum number of observations per data point, data variability, ceiling or floor effects; and (3) consider the use of a comparison group. Authors are also encouraged to discuss possible data or cointervention confounding issues and provide a rationale if no comparison group was considered. These recommendations are summarized in Table 2 and build from the Strengthening the Reporting of Observational Studies in Epidemiology statement [21].

Our systematic review is subject to some limitations related to our literature search strategy and inclusion criteria. First, we recognize that the lack of Medical Subject Headings (MeSH terms) and standardized terminology to describe the interrupted time series design may have resulted in some missed applications. Although segmented regression was first introduced to health care research in 1981 [7] and a seminal method article was published in 2002 [3], we found that many articles did not use the term "segmented regression" to describe their analysis. Therefore, particular attention to each study's statistical analysis was required during data abstraction to determine the type of interrupted time series method used. Second, our search was limited in ability to identify applications that are not indexed in either of the databases used (MEDLINE and Web of Science). Indeed, during the peer review of our article, a blind reviewer identified one eligible article [B.212] that is not indexed in the databases used and therefore was not identified in our original search.

Third, by restricting inclusion to studies that examined prescription drug utilization defined by the number or proportion of prescription drugs dispensed or patients dispensed a drug, we will have missed interrupted time series analyses with different drug outcomes, such as illicit drug use, drug sales, or drug market share [22,23]. Fourth, we acknowledge that studies examining single institution interventions (n = 59, Appendix C at www.jclinepi.com) were excluded so we could focus on population-based interventions that may be more generalizable. Despite potentially missing some applications, we feel that our results that identify an increase in the number of applications in recent years, and conclusions of the general trends of methods and underreporting of statistical considerations, would still hold. Indeed, 66% of the 59 single institution studies used segmented regression analysis, similar to our finding that 67% of studies included in our review used segmented regression analysis.

Finally, we acknowledge that our review is limited by what authors have reported or presented in their studies, which may not reflect the true methodological rigor of each study. Therefore, the large variation in reporting that we identified may not indicate inappropriate use of interrupted time series methods but rather a need for reporting standards to facilitate quality reporting, application, and interpretation of interrupted time series results.

A major strength of our systematic review is the use of multiple search strategies to identify articles. Our keyword and citation search yielded 190 eligible articles (86% overall), with only 31% identified in both. We attribute this small overlap to a lack of MeSH terms for time series analysis. The additional reference list search of eligible articles identified another 30 (14% overall) eligible applications not captured in our prior searches. This observation corroborates the importance of using multiple search strategies as identified in prior reviews of new statistical methods [17,18]. We encourage future systematic reviews to use a similar proportional Venn diagram to clarify search strategy yield.

Table 2. Methodological and reporting recommendations for interrupted time series studies[a]

Item	Item no	Recommendation
Title and abstract	1	Indicate the study design (interrupted time series) in the title or abstract
Introduction		
Background/rationale	2	Provide background regarding the intervention and setting under investigation to support the study rationale and methods
Objectives	3	(a) State specific objectives and any prespecified hypotheses (b) Distinguish between primary and secondary objectives
Methods		
Intervention	4	Define the intervention time point(s) used in the analysis
Participants	5	(a) List eligibility criteria and methods of selection (b) Define subgroups (c) Consider including a comparison group not exposed to the intervention as a secondary group of participants
Data sources and measurement	6	(a) List data source(s) (b) Comment on data completeness, validity, and changes in data coverage over time
Variables	7	(a) Define all variables • Outcome variable(s) • Descriptive and stratifying variable(s) (b) Comment on change in variable coding over time (c) Consider including details of variable coding in supplemental material, for example, appendix or research Web site
Statistical methods	8	(a) Report all statistical methods • Study time intervals, for example, monthly, quarterly • Regression model, for example, ARIMA, linear, segmented ○ For ARIMA models, indicate the intervention function, for example, point, ramp, or step ○ Indicate the appropriateness of linear model(s) when applied • Number of preintervention, postintervention, and between intervention data points (b) Define the study period and number of preintervention data points used in forecasting (c) Indicate how autocorrelation, nonstationarity, and seasonality were tested and handled (d) Consider a lag period if intervention effects are gradual or delayed (e) Define and distinguish between primary and secondary or sensitivity analyses (f) Consider use of comparison outcome(s) and/or population(s) not exposed to the intervention(s) as secondary analyses (g) Report statistical software used for analysis
Results		
Participants	9	(a) Report the number of individuals and/or observations in each group analyzed (b) Consider use of a flow diagram (c) Describe characteristics and indicate missing data
Outcome data	10	(a) Report the number of outcomes examined over the study period (b) Report the average, minimum, and maximum number of outcomes across time intervals (c) Report on data variability (d) Comment on outliers and ceiling or floor effects where relevant
Main results	11	(a) Present results using a graphical display with intervention time point(s) clearly defined (b) Consider including forecasted results graphically (c) Report absolute and/or relative change(s) and their significance, for example, clinical or policy and statistical
Other analyses	12	Report additional results (secondary and sensitivity analyses) in the article, appendix, or research Web site
Discussion		
Key results	13	Summarize key results with reference to study objectives
Context	14	(a) Provide context related to possible confounding • Discuss relevant cointerventions that occurred during the study period • Comment on the stability of participant characteristics over time • Comment on the stability of outcome coding over time (b) Discuss results of comparison analyses or provide a rationale if no comparison group was considered
Limitations	15	(a) Discuss limitations of the study (b) Comment on data variability and appropriateness of the number of data points (c) Comment on ceiling or floor effects and outliers where relevant (d) Discuss direction and magnitude of any potential bias
Interpretation	16	Provide overall interpretation of results considering objectives, limitations, results from similar studies, and other relevant evidence
Other information		
Funding	17	List funding source(s) and role of funders
References	18	Reference methodological articles that support statistical methods used

Abbreviations: ARIMA, autoregressive integrated moving average; GEE, generalized estimating equation.

[a] Items adapted from the Strengthening the Reporting of Observational Studies in Epidemiology statement [21].

In summary, we identified an increase in the number of applications of interrupted time series analysis to examine interventions in drug utilization, particularly in recent years. When properly executed, interrupted time series analysis is a valuable method to evaluate the success, failure, or unintended consequences of health care interventions on drug utilization [24]. However, there is large variation in the reporting of interrupted time series methods. Developing methodological and reporting standards for interrupted time series analysis is important to improve its application in drug utilization research. We provide a summary table of methodological and reporting recommendations for researchers to consider when completing interrupted time series analyses.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jclinepi.2014.12.018.

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