ELSEVIER

Journal of Clinical Epidemiology ■ (2015) ■

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

How many longitudinal covariate measurements are needed for risk prediction?

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Accepted 26 June 2015; Published online xxxx

Abstract

Objective: In epidemiologic follow-up studies, many key covariates, such as smoking, use of medication, blood pressure, and cholesterol, are time varying. Because of practical and financial limitations, time-varying covariates cannot be measured continuously, but only at certain prespecified time points. We study how the number of these longitudinal measurements can be chosen cost-efficiently by evaluating the usefulness of the measurements for risk prediction.

Study Design and Setting: The usefulness is addressed by measuring the improvement in model discrimination between models using different amounts of longitudinal information. We use simulated follow-up data and the data from the Finnish East–West study, a follow-up study, with eight longitudinal covariate measurements carried out between 1959 and 1999.

Results: In a simulation study, we show how the variability and the hazard ratio of a time-varying covariate are connected to the importance of remeasurements. In the East–West study, it is seen that for older people, the risk predictions obtained using only every other measurement are almost equivalent to the predictions obtained using all eight measurements.

Conclusion: Decisions about the study design have significant effects on the costs. The cost-efficiency can be improved by applying the measures of model discrimination to data from previous studies and simulations.

Keywords: Study design; Longitudinal measurements; Model discrimination; Risk prediction

1. Introduction

Epidemiologic follow-up studies usually include time-varying covariates, such as smoking, use of medication, blood pressure, cholesterol, and body mass index (BMI). Especially in long follow-up studies, these kinds of covariates may lose their predictive power over time, if only the baseline measurements are used. This can be seen as one form of the regression dilution problem [1]. An ideal solution would be to measure these covariates continuously, but this is usually impossible because of practical and financial limitations. Here we use the term ‘‘covariate’’ to mean both variables of direct interest and control variables measured on continuous or categorical scale. Longitudinal measurements carried out at prespecified time points are often used, when the speed of change in the covariates is relatively slow. Planning longitudinal measurements, however, raises many questions related to the costs and efficiency of the study. Which individuals should be measured and how frequently? Often available resources and traditions guide these decisions.

According to our knowledge, the question presented in the title has not previously been formulated as a statistical problem. In addition to the practical importance in designing an epidemiologic study, the question has also wider theoretical interest. In the general form, the question is about estimation or approximation of a stochastic continuous-time process on the basis of a small number of discrete-time observations. In the context of causal inference, the problem can be formulated as a question on the relationship between continuous-time processes and causal directed acyclic graphs [2,3]. We do not aim to solve the general problem, but to present tools that can be used to support fact-based decision making on the study design in practical situations.

Cost-efficiency of a follow-up study can be considered from different viewpoints. We assume a follow-up study

Funding: The research of J.R. was supported by the Emil Aaltonen Foundation.

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http://dx.doi.org/10.1016/j.jclinepi.2015.06.022
0895-4356/

What is new?

- The usefulness of longitudinal measurements can be systematically summarized by measures of model discrimination.
- The cost-efficiency of the follow-up study design can be improved in both ongoing and completely new follow-up studies by considering model discrimination comparisons based on simulations and data from previous studies.
- The results from the East−West study with over 50 years of follow-up suggest that carrying out covariate measurements every 10 years may by sufficient for older people when all-cause mortality is considered as an endpoint.

with time-varying covariates and a continuously observed survival outcome. Our objective was to study the determination of the reasonable number of longitudinal measurements needed for risk prediction. Another aim was to study whether a new measurement is worth carrying out in an ongoing follow-up study. We approach these questions by using simulation studies and empirical evidence from previous studies. The combination of these is also discussed.

Some other aspects of cost-efficiency of follow-up studies have already been explored. Our previous work [4] considered the optimal selection of a subset of individuals for a new measurement when we cannot afford to re-measure the entire cohort. The timing of follow-up visits has been analyzed in a case where an examination is needed to determine if an event of interest has occurred [5,6]. Optimal design of follow-up studies has also been investigated when a subset of individuals is selected for expensive genotyping [7]. In the case of longitudinal response, the optimal number of repeated measurements has been studied [8] and so-called triggered sampling design has been proposed to improve cost-efficiency [9].

Risk prediction is motivated by the need to assign interventions on the basis of the individual-level risk profiles. Before carrying out a re-examination of the covariates in an ongoing follow-up study, researchers may want to know how valuable this would be for risk prediction. This can be addressed by simulating the unknown covariate measurements and survival times and comparing the predictive abilities of a model using new measurements and a model fitted without new measurements. If the incremental benefit would be small or negligible, the re-examination could be considered to be conducted later. When we are planning a completely new follow-up study, we could use similar studies conducted earlier to learn about the importance of longitudinal measurements. By analyzing data from similar studies, we may understand better the role of re-examinations in the new study.

To evaluate the usefulness of longitudinal covariate measurements, we use measures of model discrimination [10−12] to compare models using different amounts of longitudinal information. These measures have already been applied to specific cases to show that using longitudinal covariate measurements improves model performance compared with using only baseline measurements [13,14]. In this article, we present the concepts on a general level and, in addition, study a practical example based on data from the East−West study, the Finnish part of an international follow-up study called the Seven Countries Study [15,16]. These data suit our purposes well because the Finnish cohorts have eight longitudinal measurements carried out between 1959 and 1999, and the information on mortality is available until the end of 2011.

2. Risk models and measures of model performance

2.1. Models for risk prediction

The usefulness of longitudinal covariate measurements for risk prediction depends on the risk prediction model used. Therefore, we have to define our models of interest and design the study with respect to them. Two main approaches for modeling survival time with time-varying covariates are time-dependent Cox model [17] and so-called joint modeling [18,19]. In the time-dependent Cox model, covariate values are updated at measurement times, whereas a joint model includes models for the covariate process and survival times and allows them to be associated.

Joint modeling is often preferred because time-dependent Cox models may provide biased estimates of the regression coefficients if the longitudinal process is measured with error or includes random variation that is not captured by the measurements [20]. Bias is a less serious concern in risk prediction because the calibration of the model can be checked, and if necessary, the model can be recalibrated. There are also cases where time-dependent Cox models are appropriate [21]. Furthermore, although some specialized methods have been proposed for joint modeling with multiple longitudinal covariates, including conditional score estimator [22], latent class approach [23], and Bayesian methods [24,25], the computational methods and software for multivariate joint modeling are not fully developed. For these reasons, the time-dependent Cox model was used in this work.

The choice of the type of the model has to be study specific to obtain reasonable estimates of predicted probabilities. It is also worth noticing that there are several different ways to use longitudinal measurement information in risk prediction models. New time-dependent covariates derived from the original measurements may be, for