Sleep Medicine 37 (2017) 130–134

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Adherence to continuous positive airway pressure improves attention/psychomotor function and sleepiness: a bias-reduction method with further assessment of APPLES

Tyson H. Holmes [a, *], Clete A. Kushida [b]

[a] Human Immune Monitoring Center (HIMC), Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, 299 Campus Drive, Fairchild Science Building, Stanford, CA 94305, USA
[b] Stanford Sleep Medicine Center, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 450 Broadway Street, MC 5704, Pavilion C, 2nd Floor, Redwood City, CA 94063-5704, USA

ARTICLE INFO

Article history:
Received 4 February 2017
Received in revised form
27 June 2017
Accepted 28 June 2017
Available online 14 July 2017

Keywords:
Adherence
Continuous positive airway pressure
Instrumental variables
Shrinkage estimation
Sleep apnea

ABSTRACT

Objective/background: Variable adherence to prescribed therapies for sleep disorders is commonplace. This study was designed to integrate three available statistical technologies (instrumental variables, residual inclusion, and shrinkage) to allow sleep investigators to employ data on variable adherence in the estimation of the causal effect of treatment as received on clinical outcomes.
Patients/methods: Using data from the Apnea Positive Pressure Long-term Efficacy Study (APPLES), regression adjustment for observed and unobserved confounders was applied to two primary neurocognitive outcomes, plus two measures of sleepiness. We demonstrate how to obtain estimates of reduced uncertainty for the causal effect of treatment as received for continuous positive airway pressure (CPAP) within clinical subpopulations (defined by baseline disease severity) of sleep apnea patients.
Results and conclusions: Following six months of treatment, statistically significant improvements caused by device adherence were detected for subjective sleepiness in mild, moderate, and severe disease, objective sleepiness in severe disease, and attention and psychomotor function in moderate disease. Some evidence for worsening of learning and memory due to increased adherence in moderate disease was also detected. Application to APPLES illustrates that this method can yield bias corrections for unobserved confounders that are substantial—revealing new clinical findings. Use of this fully general method throughout sleep research could sharpen understanding of the true efficacy of pharmacotherapies, medical devices, and behavioral interventions. Extensive technical appendices are provided to facilitate application of this general method.
Clinicaltrials.gov identifier NCT00051363.

1. Introduction

1.1. Conceptual background

1.1.1. Variable adherence and problem of confounders

Variable adherence to prescribed therapies for sleep disorders is widespread [1]. In sleep research, assessment of clinical response to variable adherence is sometimes made by estimating association rather than causation between treatment as received and treatment response [2]. Estimates of association can be misleading if interpreted as estimates of causation. Unlike an externally imposed factor, such as random treatment assignment within clinical trials, a patient's level of adherence is largely self-selected. Self-selection introduces confounding variables. Confounding variables compromise consistent estimation of the causal effect of treatment as received ("local average treatment effect" among adherers [3]). For instance, those who adhere more may be older and, without adjusting for the possible confounder of age, the estimate of the causal effect of treatment as received will be inconsistent. Bias exists when the expected value of a parameter estimate differs from the true value of that parameter. Roughly, an estimator is inconsistent if bias remains even as sample size grows infinitely large.

* Corresponding author. Fax: +1 650 725 0160.
E-mail addresses: tholmes@stanford.edu (T.H. Holmes), clete@stanford.edu (C.A. Kushida).

http://dx.doi.org/10.1016/j.sleep.2017.06.022
1389-9457/

1.1.2. Subpopulations and the need for reduced uncertainty of parameter estimates

Estimation bias is not the only obstacle to understanding the causal relationship between treatment as received and clinical outcome. Equally problematic is estimation uncertainty; uncertain estimates of the same parameter can differ widely in value among separate samples drawn from the same population. Uncertainty widens confidence intervals and inflates standard errors. As sample size diminishes, uncertainty increases, and uncertainty reduces statistical power.

Randomized trials in sleep research are designed to have sufficient statistical power for testing hypotheses regarding treatment effect on the primary outcome in the full sample of participants. Nevertheless, sleep investigators are often interested in testing hypotheses regarding treatment effects within subpopulations defined by baseline moderators, such as disease severity. Sample sizes within these subpopulations are often too small to provide adequate statistical power for testing treatment effects using standard statistical procedures. Estimates of treatment effects are uncertain in these subpopulations. The small sample sizes of these subpopulations likewise introduce uncertainty into estimates of the causal effect of treatment as received on clinical outcome. Special methods are required to reduce this uncertainty.

Bias and uncertainty are related. This is the statistical phenomenon of bias-variance trade-off. Namely, statistical methods that reduce bias, including correctives for confounders, can increase uncertainty of parameter estimates. In this paper, we show sleep investigators how to apply techniques that reduce uncertainty in confounder-adjusted estimates of the causal effect of treatment as received on clinical outcome within subpopulations of interest.

1.1.3. "Adherence dose response"

Throughout the remainder of this paper, we operationalize the causal effect of treatment as received as "adherence dose response." Specifically, we define "adherence dose response" as the amount and direction of change in the clinical outcome of interest caused by each unit increment of adherence.

1.2. Why reanalyze APPLES?

Here we reanalyze a dataset from the NHLBI-sponsored Apnea Positive Pressure Long-term Efficacy Study (APPLES). Our original analysis of APPLES data assessed the impact of adherence on three neurocognitive outcomes by adjusting for 102 possible confounders observed at baseline in the comparison of continuous positive airway pressure (CPAP) and sham devices [4]. However, not all confounders are observed. Consistent estimates cannot necessarily be obtained by simply adjusting for measured confounders. In application to the APPLES dataset, Holmes et al. [5] extended these results [4] in two ways. They demonstrated a method for analysis of longitudinal adherence and outcome data and that method adjusted estimates of adherence dose response for observed and unobserved confounders. Holmes et al. [5] limited analysis to a single neurocognitive outcome—Pathfinder Number Test total time (PFNT-TT). They detected improvement in PFNT-TT due to increased adherence to CPAP but not due to increased adherence to the sham device.

The analysis presented here extends previous results [4,5] in two notable respects. Estimation of adherence dose response with adjustment for observed and unobserved confounders is expanded to now include two measures of sleepiness. We have included sleepiness to demonstrate clinical breadth of application, and sleepiness is clearly a domain of interest throughout sleep research. Further, we demonstrate how to obtain estimates of adherence dose response of reduced uncertainty within clinical subpopulations of sleep-apnea patients. With these extensions from our prior work, the goal of the present study is to integrate currently available statistical technologies to provide a fully general and accessible method for estimation of adherence dose response to sleep therapies in clinical subpopulations.

1.3. Organization of paper

The remainder of this paper is organized as follows. Section 2.1 describes the APPLES dataset. Section 2.2 provides an overview of the study's statistical methods. These methods, though built from existing, proven statistical technologies, have not yet seen widespread use in sleep research. To facilitate their use, for clinical investigators who wish to apply these methods, the Online Supplement provides extensive technical guidelines and details for their collaborating statisticians. The study's results are summarized in Section 3. The paper concludes with discussion of clinical and research implications in Section 4.

2. Materials and methods

2.1. Materials

2.1.1. Data from APPLES

We begin by describing the dataset analyzed for the present study. In APPLES, double-blind randomization assigned participants to either CPAP or sham device [6]. The present study examined two neurocognitive measures, PFNT-TT and Buschke Selective Reminding Test sum recall (BSRT-SR), plus objective (Maintenance of Wakefulness Test mean sleep latency, MWT-MSL) and subjective (Epworth Sleepiness Scale total score, ESS-TS) sleepiness measures from APPLES. The third primary neurocognitive outcome from APPLES, Sustained Working Memory Test (SWMT) overall midday score, was excluded from analysis here for technical reasons outlined in the Online Supplement. Participants were assessed on the above four outcomes at baseline, two and six months post-randomization [4]. Analyses presented here are for the six-month visit only ($n = 443$ and $n = 403$ participants remaining of originally randomized to CPAP and sham devices, respectively, for 77% follow-up). This dataset contains nearly the same sample of participants as in Ref. [5] but does not include data from the two-month visit. The present study's goal was to obtain minimal-uncertainty, minimal-bias estimates of the adherence dose response on each of these four outcomes at six months. Estimates were made in each of three subpopulations defined on baseline apnea-hypopnea index (AHI, number of abnormal sleep-related breathing events per hour of sleep) values of 10–15 ($n = 113$), >15 to 30 ($n = 249$), and >30 ($n = 484$). Nightly hours of device usage (active CPAP or sham) were captured on an Encore® Pro SmartCard© monitor (Phillips Respironics® Inc., Murrysville, Pennsylvania, USA). Current analysis was on completely de-identified data. All APPLES participants provided written informed consent. The APPLES study protocol was approved by the institutional review board at each participating center. Full details for APPLES have been previously published [4,6].

2.2. Statistical methods

2.2.1. Inconsistent estimator

Each clinical outcome was regressed on average CPAP adherence over four to six months post-randomization, age, race (white vs. non-white) and gender. All participants randomized to sham were assigned zero hours for CPAP adherence except for fifteen participants. These fifteen participants had switched to active CPAP by four months. For the present analysis, they were assigned their recorded