Brief report

Distal Measurements Can Produce False Negative Results: A Prospective Secondary Analysis of a Natural History Study

Elias M. Klemperer BA^{1,2}, John R. Hughes MD^{1,2}, Shelly Naud PhD³

¹Department of Psychiatry, Vermont Center on Behavior and Health, University of Vermont, Burlington, Vermont;

²Department of Psychological Science, Vermont Center on Behavior and Health, University of Vermont, Burlington, Vermont; ³Department of Biostatistics, Vermont Center on Behavior and Health, University of Vermont, Burlington, Vermont

Corresponding Author: Elias M. Klemperer, BA, Vermont Center on Behavior and Health, University of Vermont, UHC Campus, Mailstop 482, 1 S. Prospect St., Burlington, VT 05401, USA. Telephone: 802-656-1641; Fax: 802-847-1446; E-mail: elias.klemperer@med.uvm.edu

Abstract

Introduction: Most prospective studies of quit attempts (QAs) or abstinence measure the ability of variables to predict quitting many weeks or months later. This design ignores more proximal fluctuations in the predictor that may be more relevant. The present secondary analysis compares 6-week (distal) and daily (proximal) changes in cigarettes per day (CPD) as predictors of making a QA.

Methods: Daily smokers reported CPD and QAs nightly throughout a 12-week natural history study. We provided no treatment. In the distal analysis, we tested whether reduction in CPD between baseline and 6 weeks predicted making a QA during the following 6 weeks. In the proximal analysis, we identified episodes of one or more days of $\geq 10\%$ reduction in CPD and tested whether reduction predicted making a QA on the day immediately after the reduction episode. We tested the following predictors: (1) reduction in CPD of $\geq 10\%$ (yes/no), (2) percent reduction, (3) absolute magnitude of reduction, and (4) CPD at the end of reduction.

Results: In the distal analysis, reduction did not predict making a QA. In the proximal analysis, any reduction (OR = 3.0), greater percent reduction (OR = 1.6), greater absolute reduction (OR = 1.3), and fewer CPD on the final day of an episode (OR = 11.8) predicted making a QA the next day (all $p < .001$).

Discussion: Relying on distal measurements to identify causes of a behavior may produce false-negative results. Increased use of technological advances will make assessments of the more valid proximal measurements more feasible.

Implications: This secondary analysis tested distal and proximal predictors of making a quit attempt among the same participants and found that distal tests did not, but proximal tests did predict quit attempts. Relying on distal measurements may result in false negatives.

Introduction

The development of Ecological Momentary Assessment (EMA) and Interactive Voice Recording (IVR) technologies has made daily data collection feasible.^{1,2} Frequent measurements of an independent variable allow for detailed analysis of short-term changes as proximal predictors of outcomes.³ Prior EMA studies of tobacco use found within-participant variability in daily⁴ and hourly⁵ smoking predict

later outcomes. However, we,⁶ and others,⁷ have often relied on distal measurements of changes in smoking to predict outcomes. These studies typically test whether a change in a predictor over several months prospectively predict an outcome during the following several months or abstinence several months later. Distal measurements may have ignored the influence of shorter-term fluctuations in the predictor. Proximal predictors could provide a more sensitive

test of outcomes because they allow for analyses with greater power³ or because they have closer proximity to outcomes than distal measurements. We are not aware of any prior direct comparison of the sensitivity of proximal versus distal predictors. We present findings from a secondary analysis to illustrate the differences in outcomes from distal versus proximal predictors of a QA.

Methods

We tested participants' (1) changes in cigarettes per day (CPD) over 6 weeks as a distal predictor of making a QA during the subsequent 6 weeks and (2) daily changes in CPD as proximal predictors of making a QA the next day in the same dataset. This is a secondary analysis of longitudinal data collected to study the natural history of smoking. A full description of the methodology and main findings are reported elsewhere.^{4,8} The University of Vermont Committee on the Use of Human Participants approved the study, and we registered the study at www.clinicaltrials.gov (NCT00995644).

Recruitment

During 2010 and 2011, we recruited 152 participants from Internet advertising in various major cities in the United States. Major inclusion criteria included ≥ 18 years of age and smoked ≥ 10 CPD for at least 1 year. We recruited participants who intended to probably or definitely quit sometime in the next 3 months to obtain a sample likely to change their smoking during the study period.

To ensure each participant contributed to both distal and proximal analyses, we excluded participants who (1) were not smoking at weeks 1 and 6 or (2) did not have a minimum of 7 days regular smoking at any point in the study ($n = 28$). The remaining 124 participants were mostly middle aged (mean = 45 years old, $SD = 13$), female (69%), and Caucasian (78%). At intake, participants smoked a mean of 19 CPD ($SD = 10$) and were moderately dependent (Mean Fagerstrom Test for Cigarette Dependence score = 5.4, $SD = 2.2$).

Assessment

In this natural history study, we provided no treatment. Participants reported the number of CPD smoked via an IVR system nightly for 12 weeks. If participants did not smoke on a given day, they were asked if this was an attempt to stop smoking. At the end of each week, participants were also asked whether and when they made any QAs that lasted < 1 day. We reimbursed participants to engender high compliance. We did not use biochemical verification of abstinence because verification is usually not necessary when no treatment is provided and face-to-face contact is minimal.⁹

Analysis

Data from the same 124 participants were used for both distal and proximal analyses. In our primary distal analysis, we conducted between-participant tests of whether reduction in CPD from baseline to week 6 predicted making a QA during the following 6 weeks. We used logistic regressions to examine the following predictors of the likelihood of making a QA: any reduction (ie, $\geq 10\%$) versus no reduction in CPD, mean absolute reduction in CPD, mean percent reduction in CPD, and final CPD (ie, mean CPD during week 6). In treatment studies, reduction is often defined as reducing CPD by $\geq 50\%$. However, unlike most treatment studies, it was unclear when our participants were trying to quit or change their CPD and thus we decided to include participants who reduced $\geq 10\%$ CPD for

our primary analyses. In addition, we conducted sensitivity analyses testing the same predictors among participants who reduced $\geq 50\%$ CPD. Our outcome was whether a QA of any length occurred between the beginning of week 7 and the end of week 12.

In our primary proximal analysis, we identified episodes of $\geq 10\%$ reduction in CPD that lasted one or more days ($N = 1229$). Given that each subject provided multiple episodes, multilevel logistic regression was used for the proximal analyses to account for both within- and between-participant variation. We conducted the analyses to test whether any reduction (ie, $\geq 10\%$) versus no reduction in CPD, mean absolute reduction in CPD, mean percent reduction in CPD, and final CPD on the last day of an episode predicted making a QA on the day after the reduction episode ended. In addition, we conducted two sensitivity analyses. The first was identical to that described above but used the traditional $\geq 50\%$ reduction definition. The second was done retaining only the first reduction episode from each participant (ie, 124 episodes) for a between-participant analysis of proximal predictors to assess whether our findings remained without the use of multilevel modeling or the much larger sample size used in our primary proximal analysis.

For the proximal analyses, the baseline CPD was the mean CPD across days in which participants reported no intentions to reduce or quit and were not within 1 week after a period of abstinence. Each day's change in CPD was calculated using this baseline CPD. Episodes ended when the CPD returned to $\geq 90\%$ of the participant's baseline CPD or a QA was reported. Days of abstinence were not counted as reduction or included in reduction episodes. Findings from our prior secondary analysis that used proximal predictors similar to those used in this paper are reported elsewhere.⁸ The software SAS v 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results

Distal Predictors

In the baseline to week 6 analysis, 52 of the 124 participants reduced $\geq 10\%$ CPD. Mean percent reduction was 33%, mean absolute reduction was 6.1 CPD, and the mean final CPD during week 6 was 12.8. Among participants who had any reduction, 63.5% made a QA during the following 6 weeks. Among those who did not reduce, 51.4% made a QA during the following 6 weeks. Neither (1) any reduction, (2) percent reduction, (3) absolute reduction, nor (4) mean final CPD during week 6 predicted making a QA during the 6-week follow-up (Table 1). Findings were similar in sensitivity analyses that defined reduction as reducing CPD by $\geq 50\%$. However, only 13 participants reduced $\geq 50\%$ CPD from baseline to week 6.

Proximal Predictors

In the daily measurement, 5% of the 10416 days of IVR were missing. Across the 124 participants, there were 1229 episodes of reducing CPD by $\geq 10\%$. Mean percent reduction during an episode was 28%, mean absolute reduction was 5.0 CPD, and the mean CPD on the final day of an episode was 17.9. Among episodes of any reduction, 8.3% resulted in a QA the next day. Among days of no reduction, 3% resulted in a QA the next day. Most (84%) of QAs lasted less than 24 h. Any versus no reduction, greater percent reduction, greater absolute reduction, and fewer CPD on the final day of an episode predicted making a QA the next day (Table 1). Our sensitivity analyses when reduction was defined as reducing $\geq 50\%$ CPD was limited to 259 episodes made by 87 participants. Findings were

Table 1. Distal versus Proximal Predictors of Making a Quit Attempt

	^a Distal predictors of making a QA OR (95% CI)	^b Proximal predictors of making a QA OR (95% CI)
Any versus No Reduction	1.6 (0.8 to 3.4)	3.0 (2.3 to 3.9)
^c Percent Reduction	1.1 (0.8 to 1.5)	1.6 (1.4 to 1.7)
^d Absolute Reduction	1.0 (0.8 to 1.4)	1.3 (1.2 to 1.4)
^e Final CPD	1.6 (0.3 to 8.9)	11.8 (5.2 to 26.4)

* $p < .05$; ** $p < .01$; *** $p < .001$; OR = odds ratio; CI = confidence interval; CPD = cigarettes per day; QA = quit attempt; ^aSample sizes for distal analyses were 124 participants for Any versus No Reduction and 52 participants for Percent Reduction, Absolute Reduction, and Final CPD; ^bSample sizes for proximal analyses were 5189 episodes from 124 participants for Any versus No Reduction and 1229 episodes from 124 participants for Percent Reduction, Absolute Reduction, and Final CPD; ^cOR calculated for 10% changes; ^dOR calculated for changes in 2 CPD; ^eOR calculated by comparing 1–5 CPD versus >15 CPD.

similar to our primary analyses for any versus no reduction (OR = 4.6, 95% CI = 3.1 to 6.8) and there was a nonsignificant effect in the same direction for CPD on the final day of reduction (OR = 2.2, 95% CI = 0.1 to 33.8). Neither percent reduction (OR = 1.0, 95% CI = 0.6 to 1.6) nor absolute reduction in CPD (OR = 0.9, 95% CI = 0.7 to 1.1) predicted making a QA the next day. Our between-participant sensitivity analysis included each participants' first reduction episode only. Greater percent reduction (OR = 1.3, 95% CI = 1.01 to 1.61) and fewer CPD on the final day (OR = 6.9, 95% CI = 1.2 to 40.9) predicted making a QA the day after participants' first reduction episode but greater absolute reduction did not (OR = 1.0, 95% CI = 0.9 to 1.2).

Discussion

This secondary analysis demonstrates that analyses using distal measurements produce different results from those using proximal measurements. Given the reasonable assumption that a more proximal measure of a predictor is more likely to indicate causality than a more distal measure, we believe our findings indicate that using distal measures may produce false-negative results. In our distal analysis, none of the four measures of reduction in CPD predicted making a QA. In the proximal analysis, we found convergent validity where (1) any reduction in CPD, (2) greater percent reduction, (3) greater absolute reduction, and (4) fewer CPD on the final day of an episode all predicted making a QA the next day.

In sensitivity analyses where reduction was defined as <50% CPD, distal measures again did not predict making a QA. Proximal findings were less consistent: one of four findings remained significant, one had a nonsignificant effect in a similar direction, and two showed no effect. Differences between our primary analysis of reductions $\geq 10\%$ CPD and our sensitivity analysis of reductions $\geq 50\%$ CPD could be due to the large decrease in the number of reduction episodes (from $n = 1229$ to $n = 259$) in our proximal analyses.

In the sensitivity analyses using between-participant comparisons of proximal predictors, two of three proximal predictors of making a QA were consistent with findings from our primary analyses. Thus, differences in findings from distal versus proximal predictors do not appear to be due to our use of between-participant comparisons versus multilevel modeling.

Our analysis supports prior findings that smoking is influenced by short-term changes in behavior and environment.³ For example in a prior analysis of this dataset, we identified proximal environmental cues as robust predictors of QAs.¹⁰ In addition, a number of EMA studies have identified many proximal antecedents of smoking.³ Importantly, our findings indicate that these proximal predictors' influence on smoking can be missed when the independent variable is examined as a distal predictor. Though we used day-level smoking data for this study, measurements of changes within a day could provide more valid predictors of quitting.^{11,12} Recent developments in passive detection of smoking make fine-grained measurement of changes in smoking more feasible.¹³

Limitations and Assets

One potential limitation is that we used self-selected reduction in CPD as a predictor and thus our findings may not generalize to experimenter-induced reductions or other predictors of quitting. The majority of QAs lasted a day or less; such short QAs may be limited in predicting long-term cessation.¹⁴ However, short QAs predicted longer abstinence in our prior analysis of this dataset³ and making a QA is a necessary prerequisite to cessation. Another concern is that completing nightly surveys about smoking may have increased reduction in CPD via reactivity.^{15,16} However, we have no reason to believe that such reactivity influenced the difference in ability of proximal versus distal measurements to detect effects. One of the benefits to testing proximal predictors is often increased sample size and power to detect an effect (eg, Table 1). Thus, it is unclear whether our findings were due to the proximity of predictor to outcome per se versus increased power in our proximal analyses.

To the best of our knowledge, this is the first study to test similar independent variables as both distal and proximal predictors of quitting among the same participants. In both analyses, participants' CPD and QAs were collected via nightly surveys. Thus, recall bias was minimized and did not differ between distal versus proximal analyses. Finally, we found convergent validity between four measures of reduction and included sensitivity analyses to examine outcomes using (1) a more conventional measurement of reduction and (2) similar between-participant analyses for both distal and proximal predictors.

Conclusion

This secondary analysis tested distal and proximal predictors of making a QA among the same participants and found that distal tests did not, but proximal tests did, predict QAs. Relying on distal measurements may result in false negatives. Future studies should use EMA or IVR technologies to make more valid proximal measurements.

Funding

NIDA DA-025089 and NIDA 5 T32 DA 7242-23

Declaration of Interests

EMK and SN have nothing to disclose. JRH has received consulting and speaking fees from several companies that develop or market pharmacological and behavioral treatments for smoking cessation or harm reduction and from several nonprofit organizations that promote tobacco control. He also consults for Swedish Match on their snus product and Phillip Morris on their harm-reduction products.

References

1. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol*. 2008;4:1–32.
2. Gurchich EM, Kenna GA, Leggio L. Use of novel technology-based techniques to improve alcohol-related outcomes in clinical trials. *Alcohol Alcohol*. 2013;48(6):712–719.
3. Shiffman S. Conceptualizing analyses of ecological momentary assessment data. *Nicotine Tob Res*. 2014;16 (Suppl 2):S76–S87. doi: 10.1093/ntr/ntt195.
4. Hughes JR, Solomon LJ, Naud S, Fingar JR, Helzer JE, Callas PW. Natural history of attempts to stop smoking. *Nicotine Tob Res*. 2014;16(9):1190–1198.
5. Chandra S, Shiffman S, Scharf DM, Dang Q, Shadel WG. Daily smoking patterns, their determinants, and implications for quitting. *Exp Clin Psychopharmacol*. 2007;15(1):67–80.
6. Hughes J, Lindgren P, Connett J, Nides M. Smoking reduction in the Lung Health Study. *Nicotine Tob Res*. 2004;6(2):275–280. doi: 10.1080/14622200410001676297.
7. Broms U, Korhonen T, Kaprio J. Smoking reduction predicts cessation: longitudinal evidence from the Finnish adult twin cohort. *Nicotine Tob Res*. 2008;10(3):423–427.
8. Klemperer EM, Hughes JR, Naud S. Reduction in cigarettes per day prospectively predicts making a quit attempt: a fine-grained secondary analysis of a natural history study. *Nicotine Tob Res*. 2019;21(5):648–654.
9. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. 2002;4:149–159. doi:10.1080/14622200210123581.
10. Hughes JR, Naud S, Fingar JR, Callas PW, Solomon LJ. Do environmental cues prompt attempts to stop smoking? A prospective natural history study. *Drug Alcohol Depend*. 2015;154:146–151.
11. Shiffman S, Waters AJ. Negative affect and smoking lapses: A prospective analysis. *J Consult Clin Psychol*. 2004;72(2):192–201.
12. Chandra S, Scharf D, Shiffman S. Within-day temporal patterns of smoking, withdrawal symptoms, and craving. *Drug Alcohol Depend*. 2011;117(2-3):118–125.
13. Skinner AL, Stone CJ, Doughty H, Munafò MR. StopWatch: The preliminary evaluation of a smartwatch-based system for passive detection of cigarette smoking. *Nicotine Tob Res*. 2019;21(2):257–261.
14. Partos TR, Borland R, Yong HH, Hyland A, Cummings KM. The quitting rollercoaster: How recent quitting history affects future cessation outcomes (data from the International Tobacco Control 4-country cohort study). *Nicotine Tob Res*. 2013;15(9):1578–1587.
15. McCarthy DE, Minami H, Yeh VM, Bold KW. An experimental investigation of reactivity to ecological momentary assessment frequency among adults trying to quit smoking. *Addiction*. 2015;110(10):1549–1560.
16. Shiffman S. Commentary on McCarthy *et al.* (2015): ecological momentary assessment–Reactivity? Intervention? *Addiction*. 2015;110(10):1561–1562.