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Olga A. Vsevolozhskaya


University of Kentucky, vsevolozhskaya@uky.edu

James C. Anthony

Michigan State University

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**Inter-relationships linking probability of becoming a case of nicotine dependence with
frequency of tobacco cigarette smoking**

Olga A. Vsevolozhskaya, Ph.D.¹⁻² James C. Anthony, Ph.D.^{2*}

¹Department of Biostatistics, College of Public Health, University of Kentucky, Lexingtonh KY, USA; ²Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing MI, USA

Corresponding Author*:

James C. Anthony, Ph.D

Department of Epidemiology and Biostatistics

College of Human Medicine

Michigan State University

909 Fee Road

East Lansing, MI 48824-1030

janthony@msu.edu

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ABSTRACT (205 words against max = 250)

Introduction: Once smoking starts, some tobacco cigarette smokers (TCS) can make very rapid transitions into tobacco dependence syndromes (TCD). With adjustment for smoking frequency, we posit female excess risk for this rapid-onset TCD. In a novel application of functional analysis for tobacco research, we estimate four Hill function parameters and plot TCD risk against a gradient of smoking frequency, as observed quite soon after smoking onset.

Methods: In aggregate, the National Surveys of Drug Use and Health, 2004-2013, identified 1,546 newly incident TCS in cross-sectional research, each with standardized TCD assessment.

Results: Hill function estimates contradict our apparently over-simplistic hypothesis. Among newly incident TCS males with only 1-3 recent smoking days, an estimated 1%-3% had become rapid-onset TCD cases; non-overlapping confidence intervals show lower TCD risk for females. In contrast, among daily smokers, closer to 50% of female TCS showed rapid-onset TCD, versus under 20% of male TCS, but a larger sample will be needed to confirm the apparent female excess risk at the daily smoking frequency level.

Conclusions: Smoking frequency and TCD onset become inter-dependent quite soon after TCS onset. Feedback loops are expected, and might explain a potential reversal of male-female differences across smoking frequency gradients. These novel epidemiological estimates prompt new thinking and questions about interventions.

Keywords: nicotine; cigarettes; dose-response; Hill function; drug dependence; addiction

IMPLICATIONS (56 words relative to 50-100)

In this large sample epidemiological study, with a nationally representative sample of newly incident tobacco cigarette smokers assessed cross-sectionally, we see a quite rapid onset of tobacco dependence, with an early male excess that fades out at higher levels of smoking frequency. Next steps include development of outreach and intervention for this very rapid-onset tobacco dependence.

INTRODUCTION

As gauged by epidemiological estimates for human probability of developing a drug dependence syndrome once drug use starts, nicotine and other constituents of tobacco smoke are found to be in a top rank with heroin and cocaine, although the greater environmental availability of tobacco/nicotine products is an important consideration.¹ In recent epidemiological studies of newly incident users of cocaine and other internationally regulated drugs, we harnessed a novel Hill functional analysis approach in order to characterize how estimated probabilities of becoming drug dependent soon after onset of drug use might depend upon frequency of recent drug use, with allowances for possible feedback loops.²

This report addresses tobacco, using our novel Hill function approach. Estimates are based on newly incident tobacco cigarette smokers identified via recent national surveys in the United States (US). We posit a previously advanced hypothesis for excess TCD risk among females observed shortly after smoking onset, with smoking frequency adjustments.³⁻⁸

In order to derive sufficient statistical power and precision for detection of male-female differences, we started our project with the subset of about 1500 newly incident smokers seen within three months of first cigarette. In prior work with this 3-month interval, O'Loughlin and colleagues substantiates rapidity of dependence symptom formation in 241 newly incident Canadian smokers.³

In these Hill function analyses for study of newly incident smokers and rapid-onset TCD within three months after smoking onset, we wished to push beyond simple cross-sectional plots of estimated TCD prevalence on the $y-\hat{t}$ axis versus days of recent smoking on the $x-\hat{t}$ axis, with new constraints on potential feedback loops.⁹⁻¹¹ The Hill approach is recognizable as a 'cousin' to widely used logistic regression models, with advantages explained in 'Methods'.

METHODS

Population, sampling, and the sample under study

Designating a study population of its non-institutionalized civilian community residents age 12 years and older, the US federal government conducted National Surveys on Drug Use and Health between 2004 and 2013, and produced 'NSDUH' datasets that can be downloaded via the Substance Abuse and Mental Health Data Archives (US; SAMHDA).¹² Each year's NSDUH assesses a nationally representative cross-sectional sample, as described in multiple prior NSDUH data-related publications.¹²⁻¹⁷ Each NSDUH and its informed consent protocols are reviewed and approved by cognizant institutional review boards.

Aggregated across years, NSDUH 2004-2013 Survey Data Analysis (SDA) public use dataset includes 558,703 participants, including 1,546 identified with smoking onset within 3-months of assessment, who had smoked at least once during the past 30 days, and with TCD assessment. This subset answered standardized audio computer assisted self interview (ACASI) questions about TCD, as well as days of smoking 'part or all' of a cigarette in the past 30-days (males = 703; females = 843). Additional sample characteristics, with attention to analysis weights and adjustments for complex survey designs, are presented in Supplementary Table S1.

We did not alter the TCD case definition or its standardized assessment approach as used in prior reports based on SAMHDA and NSDUH data, in order to be consistent with what others have published already. Accordingly, TCD cases either had a Nicotine Dependence Severity Score (NDSS) ≥ 2.75 or were smoking within 30 minutes after waking, or both. We return to potential TCD assessment limitations in 'Discussion'.^{18,19}

Statistical approach

As observed in the cross-sectional sample, the estimated risk of making a fairly rapid transition from the first cigarette smoked to a TCD syndrome (within a span of three months after TCS onset) was modeled via a four-parameter Hill equation. Traditionally, logistic regression (LR) fits an ‘S’-shaped curve such that the ‘S’-shaped relationship becomes linear when expressed on the logistic scale. In the LR context, the estimand is the regression slope *per se*, typically evaluated against a log odds null value of zero (or odds ratio of 1.0). In terms of this study’s subject matter, the LR regression slope estimate *per se* permits a relatively limited characterization of the degree to which the (log) odds of becoming TCD might be associated with ‘being female’ or other suspected explanatory variables.

In our alternative Hill function approach, we can do more than estimate the single LR slope parameter. The discovery process extends to four estimated parameters of the Hill equation, namely, P_{min} , P_{max} , PD_{50} and k , and we study how these four parameters might vary for male and female newly incident smokers. The resulting parameter estimates have an epidemiologically meaningful interpretation as follows: P_{min} is the estimated probability of having transitioned into rapid-onset TCD for users with a minimal number of days smoking in the past month (i.e., $x \leq 1$); P_{max} is the maximum estimated proportion of smokers with rapid-onset TCD observed in the context of a daily smoking pattern, and there is an allowance for a maximum outside of the considered range of smoking days (i.e., $x \geq 30$ days). The estimated PD_{50} is the number of smoking days after which $\left(\frac{P_{max}}{2}\right) \times 100$ of users have transitioned into rapid-onset TCD, while k is the rate of transitioning to dependence for TCS initiates at PD_{50} days of smoking observed within 0-3 months after smoking onset.

To estimate empirical rates of TCD transition probabilities in relation to the number of recent cigarette smoking days, we aggregated NSDUH data files from multiple survey years with careful attention to the NSDUH multistage (stratified cluster) sampling design variables via the “survey” R statistical package.²⁰ All 95% confidence intervals (CI) are based on a Taylor series linearization algorithm for variance estimation.²¹ Some empirical point estimates had wider CIs (due to a smaller number of responses contributing to them). To account for the influence of these higher variance points on the Hill curves, we weighted each point observation by the inverse of its variance. Vsevolozhskaya and Anthony provide additional details on the approach, including weighted residual bootstrap procedures for CI estimation.² Online documentation shows cross-tabulated estimates, as well as the R script used for Hill function estimation: (http://www.epi.msu.edu/vsevoloz/scripts/Hill_tobacco/).

RESULTS

Graphical display of the relationships under study

Figure 1 presents observed point estimates for empirical probabilities of rapid-onset TCD for males (circles) and females (diamonds), all observed within three months of smoking the first cigarette, relative to numbers of recent smoking days. The lines, solid for males and dashed for females, represent fitted ‘S’-shaped curves from Hill functions. The shaded regions depict 95% CI. With respect to the x -axis values, the depicted points are not equally spaced from 1 to 30 because when answering questions about numbers of days of smoking “part or all a cigarette” during the 30 days prior to assessment, participants did not exhaust all possible values. For example, 6-, 9-, and 11-days were never chosen. The complete list of chosen values can be seen in supplementary online materials at

http://www.epi.msu.edu/vsevoloz/scripts/Hill_tobacco/cigdepM_all.txt and

http://www.epi.msu.edu/vsevoloz/scripts/Hill_tobacco/cigdepF_all.txt).

Viewed from a distance, Figure 1 contradicts our ‘excess female risk’ hypothesis. Indeed, among newly incident TCS males with only 1-3 recent smoking days, an estimated 1%-3% had become rapid-onset TCD cases. As can be seen clearly in the magnified inset within Figure 1, there are non-overlapping confidence intervals that show lower TCD risk for the female newly incident TCS ($p < 0.05$). In contrast, at $x = 30$, among daily smokers, close to 50% of females showed rapid-onset TCD, versus fewer than 20% of males, but a larger sample will be needed to confirm the apparent female excess risk at daily smoking frequency.

Hill function parameter estimates

The Hill function parameter estimates in Table 1 quantify the relationship observed in Figure 1. To be specific, consistent with the magnified insert of Figure 1, Table 1’s estimated P_{min} is 0.0048 for newly incident TCS who smoked a minimum number of cigarettes in the month prior to assessment (95% CI = 0.0002, 0.0081). The corresponding estimate for males is 0.0191 (95% CI = 0.0085, 0.0258), such that there is no overlap of confidence intervals.

The PD_{50} and k parameter estimates for the Hill function are unremarkable, with null male-female contrasts, given largely overlapping CI. The P_{max} parameter estimates have broad CI, but the contrasting P_{max} estimates of 1.0 for females and 0.17 for males deserve note. As conveyed in relation to Figure 1, a modestly larger sample might well show that the upper bound of this male estimate is below 25% for the daily smokers, whereas the lower bound for the female daily smokers might well be discovered to be at levels above 25%.

DISCUSSION

Studying male-female differences as can be observed during the first three months after tobacco cigarette smoking onset, an early male excess in rapid-onset transition to a tobacco dependence syndrome is observed at the lowest levels of smoking frequency. A suggestion of our hypothesized female excess risk of making a rapid-onset transition into tobacco dependence can be seen in estimates for rapid-onset daily smokers, but this male-female difference is not statistically robust; larger samples will be needed to produce more definitive evidence at this daily level of smoking. Of course, replication of these findings is needed, and the best evidence most likely will come from large sample longitudinal studies or from intervention experiments, as opposed to cross-sectional research on male-female smoking behavior.

Male-female variations in the degree to which nicotine can function as a reinforcer was mentioned in our introduction, with citations to both pre-clinical and human studies. Nicotine's function as a reinforcer has been described as more prominent in female rats versus males, with greater self-administration rates.⁵⁻⁸ Supportive human estimates can be found, as in the work of O'Loughlin and colleagues who saw a female excess in occurrence of nicotine dependence symptoms among monthly, weekly and daily smokers, but not among 'sporadic' smokers.³

Before any consideration of future directions for research, some additional limitations should be mentioned, the first of which involves a left-truncation of the TCD assessment in NSDUH research. That is, TCD is assessed only when smoking has been sustained into the 30 days

prior to assessment. Another potential critique of our estimates is that the sampling and assessment plan of NSDUH is entirely cross-sectional. However, cross-sectional studies are always needed in order to design sample sizes for longitudinal and prospective research. With this study's estimates we provide a first approximation to suggest that the originating sample of non-smokers would have to be quite large in order to produce more than 700-800 newly incident smokers in each of the male-female subgroups, which then must be stratified by smoking frequency in the first month after smoking onset.

Notwithstanding limitations of this type, we judge that our study findings should be of interest. To the best of our knowledge, this is the first epidemiological study to combine (a) broadly based cross-sectional community survey sampling designed to yield nationally representative estimates, and (b) standardized assessments to permit estimation of parameters governing very rapid transition from cigarette smoking onset until development of a tobacco dependence syndrome – i.e., as seen within 0-3 months after tobacco cigarette smoking starts. The potential male-female contrast in these smoking transitions is of interest, with observed variation across two phases of smoking involvement - namely, an early phase during which males might be more liable to rapid-onset TCD, and a later phase, when daily smoking occurs in conjunction with elevated female risk of TCD.

We close with a note about interventions as might be planned very soon after onset of smoking. To be sure, these interventions might disrupt progression from first cigarette until rapid development of a dependence syndrome. Nevertheless, the sample sizes for this type of intervention research must be very large, and the design of the interventions must take into account features of intervention attractiveness and appeal that are needed to encourage newly incident smokers to stop smoking before TCD develops. Extending traditional logistic

regression analyses of intervention impact, the Hill functional analysis provides four parameters that can be examined in the evaluation of effects of novel interventions designed to be attractive and appealing to newly incident smokers, some of whom might still ignore the risk of becoming tobacco dependent. Much can be gained by studying variations in the four Hill function parameters soon after smoking onset, as compared to what can be learned by studying the LR slope estimate all by itself.

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DECLARATION OF INTERESTS

We have no conflicts of interest to declare.

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FIGURES

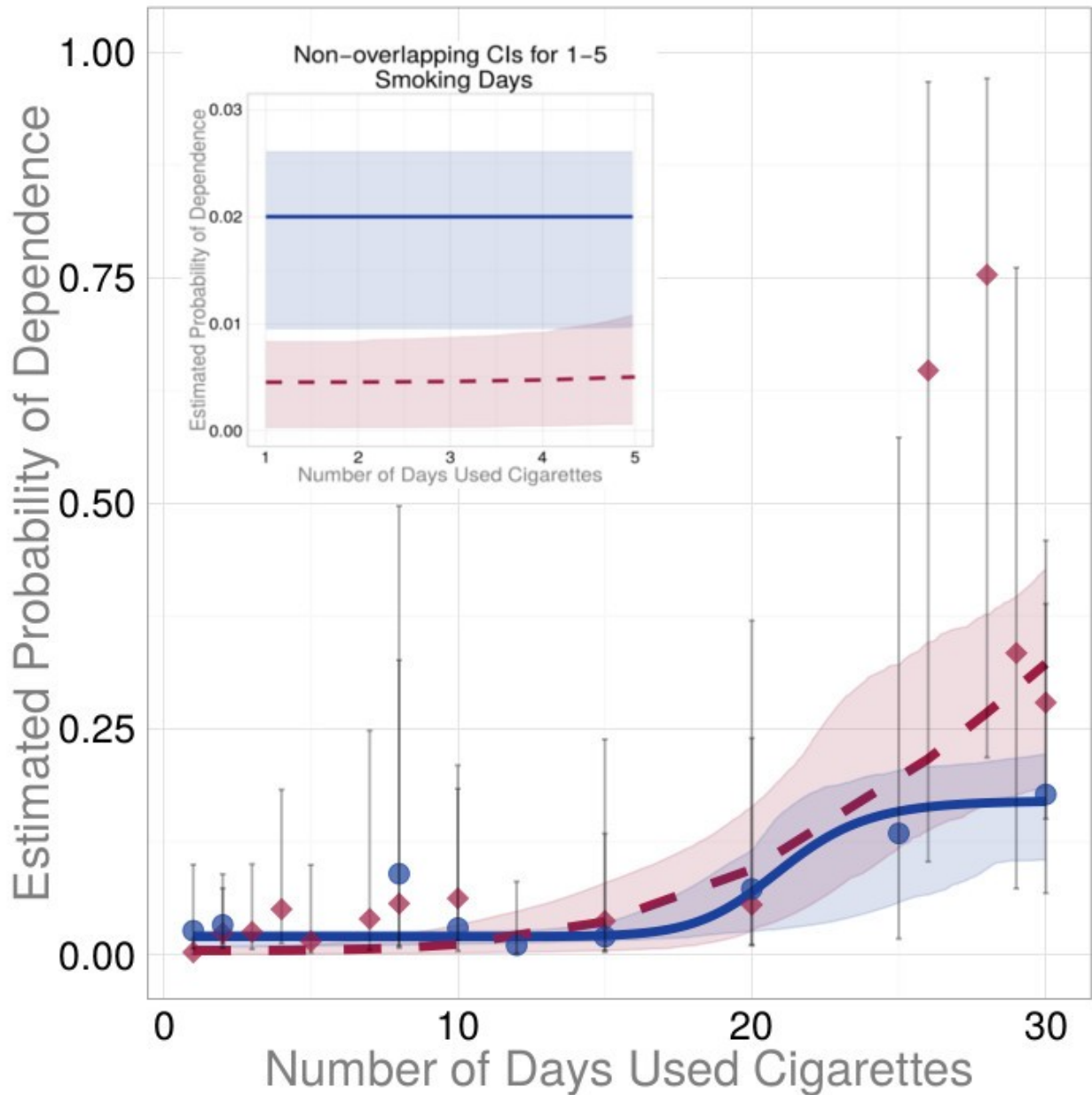


Figure 1. Estimated non-linear relationships linking number of days of tobacco cigarette smoking in the past 30 days with probability of having become tobacco dependent within three months after smoking onset. Data from the United States National Surveys on Drug Use and Health, 2004-2013. Lines represent model-fitted values of the Hill functions for males (solid) and females (dashed). Data points (circles for males and diamonds for females) represent observed proportions with dependence, and show 95% confidence intervals over the range of recent smoking days, among these newly incident tobacco cigarette smokers.

TABLES

Table 1. Hill functional analysis parameters for the estimated probability of developing rapid-onset TCD within three months after smoking onset among newly initiated tobacco cigarette smokers, expressed as a function of the number of days of smoking ‘part or all’ of a cigarette within 30 days prior to assessment, along with corresponding 95% confidence intervals. Data from the United States National Surveys on Drug Use and Health, 2004-2013.

| Estimated Hill Equation Parameters (95% Bootstrap CIs) | | | | |
|--------------------------------------------------------|----------------------------|-------------------------|---------------|----------------|
| | P_{min} | P_{max} | k | PD_{50} |
| Females (n=843)* | 0.0048 (0.0002, 0.0081) | 1.00 (0.2188, 1.000) | 4 (2, 21) | 33 (19, 51) |
| Males (n=703) | 0.0191 (0.0085, 0.0258) | 0.17 (0.1070, 1.000) | 14 (4, 99) | 21 (17, 46) |

* These are unweighted sample counts of the aggregate numbers of newly incident tobacco cigarette smokers identified in the US NSDUH nationally representative cross-sectional samples by virtue of cigarette smoking onsets within three months prior to the date of survey assessment. The parameter estimates shown in the table are analysis-weighted with 95% CI formed using variance estimation approaches appropriate for complex survey sample designs.