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Publication Date

2019-11-01

DOI

10.1016/j.addbeh.2019.106041

Peer reviewed

Accepted Manuscript

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PII: DOI: Article Number: Reference:	S0306-4603(19)30427-7 https://doi.org/10.1016/j.addbeh.2019.106041 AB 106041
To appear in:	Addictive Behaviors
Received date: Revised date: Accepted date:	11 April 2019 27 June 2019 1 July 2019

Please cite this article as: G.E. Matt, E.M. Mahabee-Gittens, J.M. Zakarian, et al., Nicotine in thirdhand smoke residue predicts relapse from smoking cessation: A pilot study, Addictive Behaviors, https://doi.org/10.1016/j.addbeh.2019.106041

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Nicotine in Thirdhand Smoke Residue Predicts Relapse from Smoking Cessation: A Pilot Study

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Keywords: Thirdhand Smoke, Nicotine, Relapse, Smoking Cessation

Abstract

<u>Introduction</u>. Thirdhand smoke (THS) residue lingers for months in homes of former smokers and may play a role in relapse after smoking cessation. This study examined the association between THS pollution as measured by the level of nicotine in house dust and continued abstinence from smoking.

<u>Methods</u>. Participants were 65 cigarette smokers who reported they were enrolled in any type of smoking cessation program, had set a specific date to quit, and had biochemical verification of continuous abstinence at 1-week (W1), 1-month (M1), 3-months (M3), or 6-months (M6) after their quit date. House dust samples collected at baseline before quitting were analyzed for nicotine concentration (μ g/g) and nicotine loading (μ g/m²) using liquid chromatography tandem mass spectrometry (LC-MS/MS).

<u>Results</u>. Controlling for age, gender, overall and indoor smoking rates, and years lived in their home, dust nicotine concentration and loading predicted abstinence at W1, M1, M3, and M6. A 10-fold increase in dust nicotine loading and concentration were associated with approximately 50% lower odds of remaining abstinent.

<u>Conclusions</u>. Findings suggest nicotine in house dust may play a role in facilitating relapse after smoking cessation. Additional research is warranted to investigate the causal role of THS residue in homes of former smokers on cravings and continued abstinence.

1. INTRODUCTION

Smoking cessation is difficult to achieve and maintain, as is evidenced by low cessation and high relapse rates especially among populations who are younger, have lower education, low income, and are racial/ethnic minorities.(Caraballo et al., 2014; Kulak, Cornelius, Fong, & Giovino, 2016; Reid et al., 2010; Simmons, Pineiro, Hooper, Gray, & Brandon, 2016; Trinidad et al., 2015) Cessation rates are lower in these groups for a many reasons including higher levels of nicotine addiction, social and cultural acceptability of smoking, low access to quitting resources, low social support to quit, financial and other stressors. (Fidler & West, 2009; Paul et al., 2010; Twyman, Bonevski, Paul, & Bryant, 2014; Wilson, Guillaumier, George, Denham, & Bonevski, 2017) Each period of resumed smoking adds to the smokers' risk of developing tobacco-related illnesses(Caraballo et al., 2014) and the risk that nonsmokers who live in their homes will experience morbidity related to tobacco smoke exposure.(Office of the Surgeon General, 2014) Thus, more research is needed to identify ways to prevent relapse after successful cessation.

A better understanding of factors that produce cravings to smoke may help former smokers remain abstinent. Research has identified a variety of cues that induce cravings including those that are visual(Conklin, Perkins, Robin, McClernon, & Salkeld, 2010; Conklin, Robin, Perkins, Salkeld, & McClernon, 2008), auditory and tactile (Erblich & Bovbjerg, 2004; McRobbie, Hajek, & Locker, 2008), and olfactory(Cortese et al., 2015; Grusser, Heinz, & Flor, 2000). These cues may be proximal in that they are part of the smoking behavior itself (e.g., cigarettes, ashtrays) or more distal, such as the environment in which smoking occurs (Conklin et al., 2010; Conklin et al., 2008). Elucidating and eliminating modifiable individual cues or combinations of cues that elicit cravings in former smokers may help to prevent relapse.(Conklin et al., 2019)

While many potential cues have been investigated, to our knowledge, no research has examined if the presence of nicotine in tobacco smoke residue (also known as thirdhand smoke, THS) (Jacob et al., 2017; Matt, Quintana, Destaillats, et al., 2011) present in the home of smokers who have quit is associated with relapse. Considering the neurophysiological properties of nicotine and the presence of high levels of nicotine in dust and on surfaces in the homes of previous smokers and smokers who have quit (Matt, Quintana, Zakarian, et al., 2011; Matt et al., 2017), we hypothesized that exposure to THS chemical constituents or THS odor may be associated with increased cravings and subsequent relapse. Specifically, we hypothesized that higher levels of THS contamination as measured by nicotine in dust are associated with higher relapse rates in smokers who have quit.

2. METHODS

Participants were 65 cigarette smokers in San Diego, California. Smokers were eligible to participate if they were ≥18 years old, reported that they were enrolled in any type of smoking cessation program and had set a specific date to quit, had lived in their home for at least six months and planned to live there for an additional six months, and were the only smokers in their home. Institutional Review Board approval was obtained from San Diego State University and the VA San Diego Healthcare System; all participants signed informed consent. Detailed methods are described elsewhere.(Matt et al., 2017) For these analyses, we included participants who: had house dust samples available at their baseline pre-quit measure, reported that no one had smoked inside their home since they quit smoking and had biochemical verification of reported continuous abstinence at 1-week (W1), 1-month (M1), 3-months (M3), or 6-months (M6) after their quit date. Participants who reported that they had resumed smoking at these timepoints were also included. Abstinence was verified with exhaled breath carbon monoxide

(CO) <5ppm. Nicotine in house dust was measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS; limit of quantitation was $0.01\mu g/g$) and is reported as nicotine concentration (nicotine per gram of dust, $\mu g/g$) and nicotine loading (nicotine per square meter, $\mu g/m^2$). The former characterizes a gram of dust with respect to its nicotine content regardless of the dustiness of a home. The latter is function of the dustiness of a home and describes the amount of nicotine present in the dust contaminating a unit area (i.e., one square meter). The dustiness of a home was operationalized as the amount of sieved dust collected per square meter (i.e., dust loading; g/m²).

To explore associations between THS pollution and smoking cessation, we conducted logistic regression analyses in which relapse and abstinence at each follow-up assessment (W1, M1, M3, and M6) were the dichotomous outcomes. Separate analyses were conducted for quit status at each timepoint and for nicotine concentration and nicotine loading. We first examined a model in which baseline levels of nicotine (log-transformed), dust loading, baseline overall smoking and indoor smoking rates, and sociodemographic variables were the predictors. We then re-estimated the model omitting nonsignificant predictors. There were no missing data. For these exploratory analyses, we set the Type I error rate at 10%.

3. RESULTS

Table 1 shows descriptive information about participants, smoking rates, and dust nicotine concentration and loading. Verified quit rates were 40% (26 of 65), 20% (13 of 65), 15% (10 of 65), and 12% (8 of 65) at W1, M1, M3, and M6, respectively. Table 2 shows baseline dust nicotine levels among abstinent and relapsed participants. Detailed information on model estimates and fit are reported in the online supplement.

At W1, number of years in residence (OR=0.91, p=0.069) and dust nicotine concentration prior to quitting (OR=0.57, p=0.030) were independently negatively associated with abstinence, and being a military veteran (OR=11.84, p=0.003) was positively associated. The same pattern was found for nicotine loading with odds ratios of 0.90 (p=0.075), 0.58 (p=0.011), and 15.81 (0.002) for the three predictor variables, respectively. With log-10 scaled dust nicotine level, an increase in nicotine loading by a factor of 10 predicted 42% lower odds of abstinence at W1. For every additional year a smoker had lived in their home, the odds of abstinence decreased by 10%. For military veterans, the odds of abstinence were 15-fold higher than for others. The overall model fit was $\chi^2(3)=13.75$ (p=0.003, Pseudo R²=0.21) for nicotine concentration and $\chi^2(3)=23.45$ (p<0.001, Pseudo R²=0.27) for nicotine loading. None of the other variables examined showed a significant association (dust loading, overall and indoor smoking rates at baseline, marital status, age, or gender). Mean baseline nicotine levels were 2.2 (concentration) and 3.4 (loading) times higher for W1 relapsed compared to W1 abstinent participants (see Table 2).

At M1, dust nicotine concentration (OR=0.53, p=0.032) was again negatively associated with successful cessation. A 10-fold higher dust nicotine concentration predicted 47% lower odds of abstinence. Being a military veteran (OR=3.67, p=0.071) was independently positively associated with abstinence, increasing the abstinence odds by a factor of 3.67. A similar pattern was found for nicotine loading with odds ratios of 0.61 (p=0.051) and 4.22 (p=0.043) for the two predictors, respectively. The overall model fit was $\chi^2(2)=10.28$ (p=0.0059, Pseudo R²=0.16) for nicotine concentration and $\chi^2(2)=9.79$ (p<0.008, Pseudo R²=0.15) for nicotine loading. None of the other variables mentioned above showed a significant association. Mean baseline nicotine

levels were 3.2 (concentration) and 3.7 (loading) times higher for M1 relapsed compared to M1 abstinent participants (see Table 2).

At M3, the significant negative association between baseline dust nicotine levels and cessation outcome continued. The odds ratios were 0.43 (p=0.012) and 0.45 (p=0.019) for concentration and loading respectively. The OR indicates that a difference in baseline dust nicotine loading by a factor of 10 lowered the odds of abstinence by 55%. The overall model fit was $\chi^2(1)=7.63$ (p=0.006, Pseudo R²=0.14) for nicotine concentration and $\chi^2(1)=8.20$ (p<0.004, Pseudo R²=0.15) for nicotine loading. None of the other variables showed a significant association. Mean baseline nicotine levels were 3.5 (concentration) and 5.6 (loading) times higher for M3 relapsed compared to M3 abstinent participants (see Table 2).

At M6, the negative association between baseline dust nicotine levels and cessation outcome were 0.57 (p=0.088) and 0.47 (p=0.039) for concentration and loading, respectively. The magnitude of the odds ratio showed a similar reduction in the odds of remaining abstinent at 43% and 53%, respectively. The overall model fit was $\chi^2(1)=3.16$ (p=0.076, Pseudo R²=0.08) for nicotine concentration and $\chi^2(1)=6.27$ (p<0.012, Pseudo R²=0.13) for nicotine loading. Mean baseline nicotine levels were 2.4 (concentration) and 5.6 (loading) times higher for M6 relapsed compared to M6 abstinent participants (see Table 2).

4. DISCUSSION

Independent of sociodemographic variables, dust loading, indoor and total smoking rates at baseline, and number of years living in the home, nicotine in settled house dust prior to cessation predicted relapse from 1 week to 6 months. At each time point, a 10-fold difference in nicotine concentration and loading (approximately the difference between 1st and 3rd quartiles) was associated with approximately 50% lower odds of successful abstinence or a doubling of the

odds of relapse. Because we statistically controlled for dust loading (grams of sieved dust collected per m²), the association between dust nicotine and relapse does not appear to be confounded with the dustiness of homes. The robust association between dust nicotine and relapse controlling for total and indoor smoking rates at baseline suggests that dust nicotine is not merely a proxy for smoking history or level of addiction. These findings are consistent with existing research on the role of cues in relapse (Conklin et al., 2019; Conklin et al., 2010; Conklin et al., 2008; Cortese et al., 2015; Grusser et al., 2000), pointing to potential biochemical or sensory connections between relapse and the persistent pollution of a smoker's home environment with nicotine and potentially other THS compounds present in dust. The exact mechanism by which THS in dust affects relapse through inhalation, dermal, and ingestion routes are currently unknown. We measure nicotine here as a marker of THS, but the cues may be from other closely associated compounds in THS. (Jacob et al., 2017; Matt, Quintana, Destaillats, et al., 2011) Our preliminary findings should be replicated in future studies and further strengthened with more detailed investigations of the mediational and moderating role of THS constituents by measuring multiple THS compounds and THS exposure among former smokers after quit attempts.

As this was an observational study of the outcomes of quit attempts associated with a range of different cessation programs, the causal association between nicotine in dust and cessation outcome should be interpreted with caution. While we statistically controlled for several plausible confounders, only a randomized experiment could conclusively rule out alternative interpretations. This study relied on a relatively small convenience sample limiting its statistical power and generalizability to other populations. Additionally, we did not evaluate potential combinations and interactions of environmental or other cues that may have been present in the

participants' homes. Limitations notwithstanding, the association of nicotine levels in settled house dust and relapse to smoking suggests that in addition to known cues that contribute to relapse (e.g., visual, environmental), THS pollution in a former smoker's home may adversely affect short- and longer-term cessation outcomes. In addition to the removal of established smoking cues, quitters may also benefit from home cleaning efforts that reduce THS pollutants from dust and other reservoirs (e.g., carpets, upholstery, surfaces). Future work with larger samples and experimental controls are needed to further examine these possible associations.

Author Disclosure

Role of Funding Sources

This research was supported by funds from the California Tobacco-Related Disease Research Grants Program Office of the University of California, Grant Number 19CA-0164. Tobacco-Related Disease Research Program, University of California, Office of the President, 300 Lakeside Drive, Sixth floor, Oakland, California, 94612-3550, USA.

Contributorship

GEM and PJEQ conceptualized and designed the original study. GEM conceived of the research idea of this paper. PJEQ and JMZ designed field sampling protocols. JMZ and GEM designed the personal interviews. MM assisted with recruitment. JMZ managed data collection, data entry, cleaning and archiving. EH supervised laboratory analyses. GEM developed the data analysis plan and conducted the data analyses. PJEQ, MM-G, EH, JMZ, and MM provided input on analyses and interpretation of data. GEM and MM-G drafted the manuscript. All authors contributed to the editing of the manuscript drafts, and GEM prepared the final version.

Conflict of Interests

The authors declare that they have no conflicts of interest.

References

- Caraballo, R. S., Kruger, J., Asman, K., Pederson, L., Widome, R., Kiefe, C. I., . . . Jacobs, D.
 R., Jr. (2014). Relapse among cigarette smokers: the CARDIA longitudinal study 1985-2011. *Addict Behav*, 39(1), 101-106. doi:10.1016/j.addbeh.2013.08.030
- Conklin, C. A., McClernon, F. J., Vella, E. J., Joyce, C. J., Salkeld, R. P., Parzynski, C. S., &
 Bennett, L. (2019). Combined Smoking Cues Enhance Reactivity and Predict Immediate
 Subsequent Smoking. *Nicotine Tob Res*, 21(2), 241-248. doi:10.1093/ntr/nty009
- Conklin, C. A., Perkins, K. A., Robin, N., McClernon, F. J., & Salkeld, R. P. (2010). Bringing the real world into the laboratory: personal smoking and nonsmoking environments. *Drug Alcohol Depend*, *111*(1-2), 58-63. doi:10.1016/j.drugalcdep.2010.03.017
- Conklin, C. A., Robin, N., Perkins, K. A., Salkeld, R. P., & McClernon, F. J. (2008). Proximal versus distal cues to smoke: the effects of environments on smokers' cue-reactivity. *Exp Clin Psychopharmacol*, 16(3), 207-214. doi:10.1037/1064-1297.16.3.207
- Cortese, B. M., Uhde, T. W., LaRowe, S. D., Stein, S. V., Freeman, W. C., McClernon, F. J., . . . Hartwell, K. J. (2015). Olfactory cue reactivity in nicotine-dependent adult smokers. *Psychol Addict Behav*, 29(1), 91-96. doi:10.1037/adb0000018
- Erblich, J., & Bovbjerg, D. H. (2004). In vivo versus imaginal smoking cue exposures: is seeing believing? *Exp Clin Psychopharmacol*, *12*(3), 208-215. doi:10.1037/1064-1297.12.3.208
- Fidler, J. A., & West, R. (2009). Self-perceived smoking motives and their correlates in a general population sample. *Nicotine Tob Res*, *11*(10), 1182-1188. doi:10.1093/ntr/ntp120
- Grusser, S. M., Heinz, A., & Flor, H. (2000). Standardized stimuli to assess drug craving and drug memory in addicts. *J Neural Transm (Vienna)*, 107(6), 715-720. doi:10.1007/s007020070072

- Jacob, P., 3rd, Benowitz, N. L., Destaillats, H., Gundel, L., Hang, B., Martins-Green, M., . . . Whitehead, T. P. (2017). Thirdhand Smoke: New Evidence, Challenges, and Future Directions. *Chem Res Toxicol*, 30(1), 270-294. doi:10.1021/acs.chemrestox.6b00343
- Kulak, J. A., Cornelius, M. E., Fong, G. T., & Giovino, G. A. (2016). Differences in Quit Attempts and Cigarette Smoking Abstinence Between Whites and African Americans in the United States: Literature Review and Results From the International Tobacco Control US Survey. *Nicotine Tob Res, 18 Suppl 1*, S79-87. doi:10.1093/ntr/ntv228
- Matt, G. E., Quintana, P. J., Destaillats, H., Gundel, L. A., Sleiman, M., Singer, B. C., ...
 Hovell, M. F. (2011). Thirdhand tobacco smoke: emerging evidence and arguments for a multidisciplinary research agenda. *Environ Health Perspect*, *119*(9), 1218-1226.
 doi:10.1289/ehp.1103500
- Matt, G. E., Quintana, P. J., Zakarian, J. M., Fortmann, A. L., Chatfield, D. A., Hoh, E., . . .
 Hovell, M. F. (2011). When smokers move out and non-smokers move in: residential thirdhand smoke pollution and exposure. *Tobacco Control*, 20(1), e1. doi:10.1136/tc.2010.037382
- Matt, G. E., Quintana, P. J. E., Zakarian, J. M., Hoh, E., Hovell, M. F., Mahabee-Gittens, M., . . .
 Chatfield, D. A. (2017). When smokers quit: exposure to nicotine and carcinogens persists from thirdhand smoke pollution. *Tobacco Control*, 26(5), 548-556.
 doi:10.1136/tobaccocontrol-2016-053119
- McRobbie, H., Hajek, P., & Locker, J. (2008). Does the reaction of abstaining smokers to the smell of other people's cigarettes predict relapse? *Addiction*, 103(11), 1883-1887. doi:10.1111/j.1360-0443.2008.02340.x

- Office of the Surgeon General. (2014). *The health consequences of smoking--50 years of progress : a report of the surgeon general*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General.
- Paul, C. L., Ross, S., Bryant, J., Hill, W., Bonevski, B., & Keevy, N. (2010). The social context of smoking: A qualitative study comparing smokers of high versus low socioeconomic position. *BMC Public Health*, 10, 211. doi:10.1186/1471-2458-10-211
- Reid, J. L., Hammond, D., Boudreau, C., Fong, G. T., Siahpush, M., & Collaboration, I. T. C. (2010). Socioeconomic disparities in quit intentions, quit attempts, and smoking abstinence among smokers in four western countries: findings from the International Tobacco Control Four Country Survey. *Nicotine Tob Res, 12 Suppl*, S20-33. doi:10.1093/ntr/ntq051
- Simmons, V. N., Pineiro, B., Hooper, M. W., Gray, J. E., & Brandon, T. H. (2016). Tobacco-Related Health Disparities Across the Cancer Care Continuum. *Cancer Control*, 23(4), 434-441. doi:10.1177/107327481602300415
- Trinidad, D. R., Xie, B., Fagan, P., Pulvers, K., Romero, D. R., Blanco, L., & Sakuma, K. L.
 (2015). Disparities in the Population Distribution of African American and Non-Hispanic
 White Smokers Along the Quitting Continuum. *Health Educ Behav*, 42(6), 742-751.
 doi:10.1177/1090198115577376
- Twyman, L., Bonevski, B., Paul, C., & Bryant, J. (2014). Perceived barriers to smoking cessation in selected vulnerable groups: a systematic review of the qualitative and quantitative literature. *BMJ Open*, 4(12), e006414. doi:10.1136/bmjopen-2014-006414
- Wilson, A., Guillaumier, A., George, J., Denham, A., & Bonevski, B. (2017). A systematic narrative review of the effectiveness of behavioural smoking cessation interventions in

selected disadvantaged groups (2010-2017). Expert Rev Respir Med, 11(8), 617-630.

doi:10.1080/17476348.2017.1340836

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<u>Table 1</u>: Participants' sociodemographic background, smoking rates, and overall dust loading, dust nicotine concentration, and dust nicotine loading (N=65). Additional information about baseline dust nicotine levels among abstinent and relapsed participants is provided in Table 2.

Age (Years; Q1-Mdn-Q3)	44 - 50 - 55	
Income (\$1,000; Q1-Mdn-Q3)	12 - 20 - 30	
Years at residence (Q1-Mdn-Q3)	1 - 2 - 6	Q
Female (%)	48	
Employment (%)	Ċ	
Part-time	16	
Fulltime	12	
Not employed	72	
Military Veteran (%)	21	
Ethnic/Racial Background (%)		
Black/African-American	43	
White	40	
Latino/Hispanic	9	
Multi-racial	6	
Baseline Smoking Rate (Q1-Mdn-		
Q3)	60 - 89 - 140	
Total (cigarettes/week)	26 - 50 - 90	
Indoors (cigarettes/week)		
Baseline Dust (Q1-Mdn-Q3)		
Dust Loading (g/m ²)	0.14 - 0.47 - 1.71	
Nicotine Concentration (µg/g)	5.1 - 25.1 - 54.5	
Nicotine Loading (µg/m ²)	2.0 - 6.3 - 33.9	
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<u>Table 2</u>: Geometric means and 95% confidence intervals of baseline dust nicotine loading and concentration for abstinent and relapsed participants 1 week, 1 month, 3 months, and 6 months after their quit date.

		Baseline Nicotine	
		Loading (µg/m ²)	Concentration ($\mu g/g$)
	Ν	Geo Mean [95% CI]	Geo Mean [95% CI]
Week 1			
Abstinent	26	3.3 [1.5;7.5]	10.0 [5.8;17.2]
Relapse	39	11.1 [5.5;22.3]	22.0 [14.2;34.3]
Month 1			0
Abstinent	13	2.4 [0.9;5.5]	6.4 [2.8;14.8]
Relapse	52	8.9 [4.9;16.2]	20.2 [14.0;29.2]
Month 3			
Abstinent	10	1.6 [0.6;4.2]	5.5 [2.6;11.6]
Relapse	55	8.9 [5.0;15.9]	19.5 [13.4;28.3]
Month 6		\sim	
Abstinent	8	1.5 [0.5;5.2]	7.5 [3.6;16.0]
Relapse	57	8.4 [4.8;14.8]	17.8 [12.2;26.1]
R CK			

Highlights

- Thirdhand smoke (THS) remains in homes of smokers after they quit.
- House dust nicotine before quitting predicts relapse up to 6 months after quitting.
- A ten-fold increase in dust nicotine was associated with 50% lower odds of quitting.
- THS in the homes of former smokers may play a role in relapse after cessation.

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Conflict of Interests

The authors declare that they have no conflicts of interest.

Joseph Contraction of the second