Association Between Initiation of ENDS and Cigarette Smoking Reduction: A Causal Time Zero Approach to the PATH Study

Anna Dumas, BS, Shaloo Gupta, MS, Chris Freehauf, BS, Jenny Cai, MBA MA, Felix Marczykowski, MSc, Claudia Kanitscheider, MA, Jason Kennedy, MS

Oracle Life Sciences, Austin, TX, USA

Background

- Cigarette smoking remains a major public health concern and is one of the leading causes of preventable deaths
- Smoking-related illnesses contribute to over 8 million deaths worldwide annually, with more than 480,000 deaths per year in the United States alone, by CDC and WHO estimates
- A variety of nicotine products such as electronic nicotine delivery systems (ENDS) are available for smokers who do not want to quit using nicotine completely, but want to reduce their exposure to harmful constituents present in cigarette smoke due to combustion
- Long-term effects of ENDS on smoking behavior remains uncertain, with most studies relying on descriptive analysis or short-term follow up times, limiting their ability to establish causal relationships

Objective

- To understand the causal relationship between ENDS initiation and cigarette consumption
- To improve on prior estimates of ENDS impact with the use of target trial emulation and directed acyclic graphs

Methods

Dataset: Population Assessment of Tobacco and Health (PATH) study
- Nationally representative longitudinal cohort designed to assess tobacco use behaviors
- Assessed 2013-2019

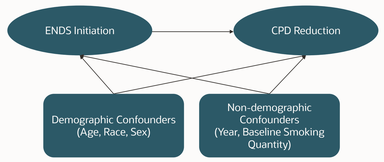
Inclusion criteria: Adult participants who were exclusive cigarette smokers in their first year of participation

Primary exposure: ENDS initiation, defined as the first self-reported use of ENDS at any follow-up wave after baseline

Primary outcome: Cigarette consumption changes from year prior, measured two ways:
- Continuous change in cigarettes per day (CPD)
- Binary indicator of achieving 50% reduction in CPD

Statistical model: Causal time-zero approach within a target trial emulation framework:
- Multilevel mixed-effects linear and logistic regression
- Fixed effects: ENDS initiation, age, sex, race, baseline cigarette smoking quantity
- Random effects: Participant, participant year
- Participants contributed person-year observations while they remained exclusive cigarette smokers
- The year of ENDS initiation was treated as 'time zero'
- CPD is calculated based on reported cigarette consumption at the time of survey
- Participants data were censored from models in years after ENDS initiation

Figure 1. Directed acyclic graph (DAG) Illustrating Potential Confounding in the Relationship Between ENDS Initiation and Smoking Reduction



What is causal time-zero?

- Methodological framework designed to improve causal inference in observational studies by aligning the start of follow-up that mimics an randomized controlled trial (RCT)
- Directed acyclic graphs (DAGS) are used to visualize relationships between variables
- Used framework to evaluate the impact of ENDS initiation on cigarette consumption by ensuring participants were classified into exposure and control groups based on their first opportunity to initiate ENDS
- To quantify this relationship, we used:
  - Linear regression to estimate the effects of ENDS initiation on continuous changes in CPD, adjusting for key covariates
  - Logistic regression models assessed the likelihood of achieving a ≥50% reduction in CPD, adjusting for key covariates

Results

- Among 52,433 adult participants, 3,388 met criteria for inclusion who were ENDS naïve and smoked ¼ a pack a day on average with an average follow up time of 2 years
- 33.7% participants who initiated ENDS use experienced a mean CPD reduction of 2.11 CPD along with a 1.31-fold increase in the odds of achieving ≥50% CPD reduction compared to exclusive cigarette smokers

Figure 2. Selection of Exclusive Cigarette Smokers for Longitudinal ENDS Initiation Analysis (2013–2019 PATH Study)

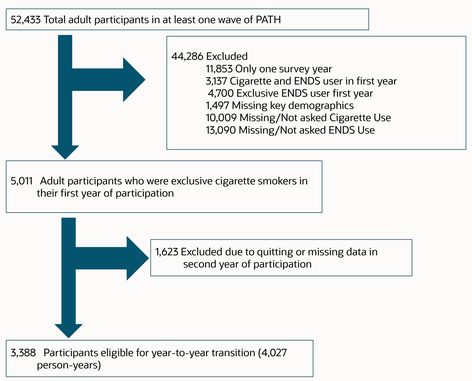


Table 1. Participants who initiated and did not initiate ENDS were demographically similar at baseline

	Participants who did not initiate ENDS	Participants who initiated ENDS	Overall
	N= 2,246	N= 1,142	N= 3,388
Age Category, N (%)			
18 to 34 years old	1651 (73.5%)	868 (76.0%)	2519 (74.4%)
35-55 years old	509 (22.7%)	254 (22.2%)	763 (22.5%)
55 years old or older	86 (3.8%)	20 (1.8%)	106 (3.1%)
Sex, N (%)			
Male	1110 (49.4%)	592 (51.8%)	1702 (50.2%)
Female	1136 (50.6%)	550 (48.2%)	1686 (49.8%)
Race, N (%)			
White	1727 (76.9%)	908 (79.5%)	2635 (77.8%)
Black	255 (11.4%)	103 (9.0%)	358 (10.6%)
Other	222 (9.9%)	117 (10.2%)	339 (10.0%)
Missing	42 (1.9%)	14 (1.2%)	56 (1.7%)
Education, N (%)			
HS Graduate or less, Missing	1096 (48.8%)	631 (55.3%)	1727 (51.0%)
Some college or Advanced Degree	1150 (51.2%)	511 (44.7%)	1661 (49.0%)
Census Region, N (%)			
Northeast	322 (14.3%)	160 (14.0%)	482 (14.2%)
Midwest	631 (28.1%)	282 (24.7%)	913 (26.9%)
South	808 (36.0%)	425 (37.2%)	1233 (36.4%)
West	452 (20.1%)	209 (18.3%)	661 (19.5%)
Unknown	33 (1.5%)	66 (5.8%)	99 (2.9%)

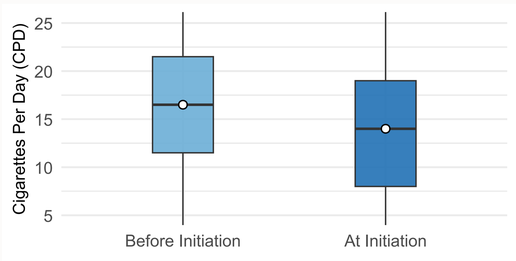
Table 2. Quantity of cigarettes smoked and nicotine dependence characteristics were comparable across groups at baseline

	Participants who did not initiate ENDS	Participants who initiated ENDS	Overall
	N= 2,246	N= 1,142	N= 3,388
Cigarette Quantity Smoked Per Day, N (%)			
Less than half a pack (less than 10 cigarettes)	1265 (56.3%)	622 (54.5%)	1887 (55.7%)
Half a pack to a full pack (10 to 20 cigarettes)	779 (34.7%)	410 (35.9%)	1189 (35.1%)
More than a full pack (more than 20 cigarettes)	202 (9.0%)	110 (9.6%)	312 (9.2%)
Time to First Cigarette After Waking (Minutes)			
Mean (SD)	90.0 (162)	67.6 (129)	82.4 (152)
Median [Min, Max]	30.0 [0, 1200]	20.0 [0, 1080]	30.0 [0, 1200]
Missing, N (%)	218 (9.7%)	102 (8.9%)	320 (9.4%)

Discussion

- Previous PATH-based studies have found that more frequent ENDS use is associated with reduced cigarette use (aOR: 2.32; 95% CI: 1.38–3.90), and daily ENDS use is associated with higher cigarette discontinuation rates (e.g., aOR: 2.26; 95% CI: 1.34–3.81)
- However, these analyses often relied on logistic models within single survey years or year-to-year transitions, limiting their ability to assess the longer-term impact and timing of ENDS initiation
- Our study findings align with this prior research but offer a more robust estimate due to the application of a causal time-zero framework

Figure 3. Comparing self-reported cigarette use in the years before and at ENDS initiation among participants who initiated ENDS using median CPD

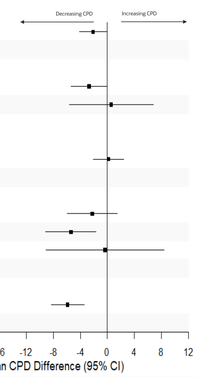


Strengths/Limitations

- The causal time-zero design improves internal validity and mimics trial conditions in observational data
- Longitudinal PATH datasets allowed for multi-year tracking of smoking behavior
- These findings are based on self-reported data from a single cohort (PATH), which may not generalize to all populations
- Data are cross sectional thus knowing exact time of ENDS initiation is not possible
- As with all observational studies, unmeasured confounding may remain, and RCTs are still the strongest design for causal inference

Figure 4. ENDS Initiators Experienced Greater Reductions in CPD Than Non-Initiators, After Adjusting for Baseline Characteristics in Multivariable Linear Regression

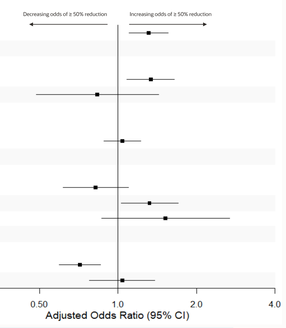
Predictor	Adj. Estimate	95% CI
ENDS Initiation:		
ENDS Initiated	-2.11	-4.15 to -0.07
Age:		
35–54 (Reference)		
18–34	-2.70	-5.39 to -0.01
55+	0.57	-5.66 to 6.80
Sex:		
Female (Reference)		
Male	0.17	-2.06 to 2.40
Race:		
White (Reference)		
Black	-2.24	-5.94 to 1.46
Other	-5.41	-9.13 to -1.69
Missing	-0.34	-9.08 to 8.40
Baseline CPD:		
Less than 10 cigarettes (Reference)		
10 to 20 cigarettes	-5.89	-8.34 to -3.44
More than 20 cigarettes	-23.19	-27.27 to -19.11



Footnote: Coefficients were adjusted for age, sex, race, and baseline CPD

Figure 5. ENDS Initiation Was Associated With Increased Odds of Reducing Cigarette Use by 50% or More in Multivariable Logistic Regression

Predictor	aOR	95% CI
ENDS Initiation:		
ENDS Initiated	1.31	1.10 to 1.56
Age:		
35–54 (Reference)		
18–34	1.33	1.08 to 1.64
55+	0.83	0.48 to 1.43
Sex:		
Female (Reference)		
Male	1.04	0.88 to 1.22
Race:		
White (Reference)		
Black	0.82	0.62 to 1.10
Other	1.32	1.03 to 1.70
Missing	1.52	0.87 to 2.68
Baseline CPD:		
Less than 10 cigarettes (Reference)		
10-20 cigarettes	0.71	0.59 to 0.86
More than 20 cigarettes	1.04	0.78 to 1.38



Footnote: Coefficients were adjusted for age, sex, race, and baseline CPD

Conclusion

- ENDS initiation is associated with a significant reduction in cigarette consumption among exclusive cigarette smokers
- ENDS initiators showed a greater reduction in CPD compared to non-initiators
- Casual approach may be useful to understand causal relationships and longitudinal datasets
- Further research in diverse populations and over longer follow-up periods is needed to confirm and expand on these results

References

- Hernán, M. A., Wang, W., & Leaf, D. E. (2022). Target trial emulation. JAMA, 328(24), 2446. https://doi.org/10.1001/jama.2022.21383
- Kasza, K. A. et al. (2024). E-Cigarette characteristics and cigarette cessation among adults who use e-cigarettes. JAMA Network Open, 7(8), e2423960. https://doi.org/10.1001/jamanetworkopen.2024.23960
- Sharma, E. et al. (2024). Cigarette and ENDS dual use longitudinal transitions among adults in the Population Assessment of Tobacco and Health (PATH) Study, Waves 4–5 (2016–2019). Addictive Behaviors Reports, 19, 100528. https://doi.org/10.1016/j.abrep.2024.100528

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