Received: 13 April 2022 | Revised: 31 May 2022 | Accepted: 15 June 2022

DOI: 10.1002/dta.3335

RESEARCH ARTICLE

WILEY

Examination of the impact of *my*blu electronic nicotine delivery system e-liquid nicotine strength on self-reported measures of dependence

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Funding information
This work was funded by Fontem US LLC, a subsidiary of Imperial Brands PLC and manufacturer of the *my*blu™ products assessed in this study. This work was contracted by Imperial Brands PLC as a service provider on behalf of Fontem US LLC. Study design and data collection were performed independently of the study sponsor.

Abstract

Background: Greater nicotine delivery is associated with higher nicotine concentrations in electronic nicotine delivery system (ENDS) liquids. However, there is a current debate as to whether this leads to increased dependence and mitigates ENDS public health potential.

Methods: Self-reported dependence among users of *my*blu ENDS containing different nicotine concentrations was examined with data from a multiwave cross-sectional survey of US young adults and adults. Questions examined responses related to dependence measures and participants' most often used *my*blu ENDS nicotine concentration (low: 0%, 1% and 1.2%; medium: 2%, 2.4% and 2.5%; or high: 3.6% and 4%).

Results: A global general linear model using nicotine concentration, age and days *my*blu that was used in the past 30 revealed a significant difference in PROMIS scores among nicotine concentration groups ($F = 4.07$, $p = 0.02$). However, pairwise comparisons to examine which specific groups differed significantly from others showed no significant differences. Logistic regression demonstrated that strong past 30-day cravings to use *my*blu among participants using high or medium nicotine concentrations were not significantly different from those using a low concentration (ORs 0.66 [0.42, 1.03], $p = 0.07$ and 0.95 [0.49, 1.82], $p = 0.98$, respectively). Time to daily first use for high or medium nicotine concentration users was not significantly different from those using a low concentration (ORs 0.89 [0.70, 1.14], $p = 0.35$ and 0.84 [0.57, 1.25], $p = 0.40$, respectively).

Conclusions: Use of *my*blu ENDS with different nicotine concentrations is not associated with differing levels of dependence. Our findings contradict the notion that high ENDS e-liquid nicotine levels generate increased dependence.

KEYWORDS
cigarette smoking, dependence, e-cigarettes, ENDS, nicotine

1 | INTRODUCTION

Smoking combustible cigarettes is a cause of serious disease in smokers including lung cancer, heart disease and emphysema.[1] Smoking is reported to directly cause more than 7 million deaths per year globally,[2] and in the United States of America (USA) almost 500,000 annual deaths can be attributed to cigarette smoking.[3] While quitting smoking greatly reduces disease risk[1] and despite large numbers of adult smokers wanting to stop smoking,[4] less than 10% of adult smokers actually stop smoking each year.[4] In those adult smokers who are uninterested or unwilling to quit smoking and who would otherwise continue to smoke cigarettes, a number of public health bodies such as Public Health England, the UK Royal College of Physicians, the New Zealand Ministry of Health and Health Canada have proposed that reduced exposure products such as electronic nicotine delivery systems (ENDS) may provide a less harmful alternative to cigarette smoking and therefore support tobacco harm reduction efforts.[5–8] It is important, however, to consider how tobacco harm reduction at a population level may be achieved. Only if the potential reduction in product use risk is coupled with uptake by sufficient populations of current adult smokers who would otherwise continue to smoke, and minimal uptake by nicotine-naïve users and unintended groups like youth, can population harm reduction be maximised.

While not unequivocal, data from interventional studies have shown ENDS to be effective in supporting smoking cessation[9–13] although some data suggest only certain circumstances (e.g., daily and nonintermittent use) under which ENDS use is effective in supporting cessation.[14–16] Observational data also support a link between ENDS use and quitting smoking.[14,16–21] Furthermore, reductions in smoking prevalence supported by exclusive ENDS use may translate into large improvements in population health by reducing smoking-related mortality.[22,23] It has been proposed that ENDS that have nicotine pharmacokinetic characteristics closer to combustible cigarettes are likely to be more effective in helping adult smokers transition away from cigarette smoking,[24] potentially due to cigarette-like nicotine delivery as well as comparable behavioural and sensorial effects. Similar effects have been reported for other nicotine products, with improved nicotine delivery profiles associated with better smoking cessation support and relapse prevention.[25,26] However, greater nicotine delivery and more cigarette-like pharmacokinetics are often associated with higher concentrations of nicotine in ENDS liquids.[24,27–31] This has led to the suggestion that higher e-liquid nicotine levels can lead to increased dependence on ENDS,[32,33] which may mitigate their public health potential. One recent study assessed dependence as a function of estimated aerosol nicotine yield, finding a difference in dependence between low and high extremes. However, when assessed as a function of nicotine content, no differences in dependence were observed.[33] Aside from this study, there is no information in the literature to determine whether users of higher e-liquid concentrations of nicotine are more dependent on ENDS use.

blu ENDS, including *my*blu, are marketed in the United States and elsewhere as an alternative to smoking cigarettes for current adult smokers. *my*blu ENDS are commercially available in the United States in two forms (*my*blu and *my*blu Intense), both of which contain different levels of nicotine either in its 'freebase' form (*my*blu) at concentrations between 1% and 2.4% or in the form of a nicotine lactate salt formulation,[30] with concentrations between 2.4% and 4% (*my*blu Intense). While other studies have assessed dependence for a broad range of ENDS device types, this is a potential limitation since different device features and e-liquid compositions give rise to different yields of nicotine in the aerosol even when they contain the same nicotine concentration[34–36] and therefore provide different nicotine delivery to users. Thus, the availability of a wide range of nicotine concentrations in *my*blu ENDS presents the potential to assess, independently of device type, whether users of higher ENDS nicotine concentrations are any more dependent than users of lower nicotine concentrations, and to specifically address the question of whether the use of higher concentrations of nicotine in ENDS is associated with greater self-reported dependence. To meet this need, we have assessed data from three waves of a cross-sectional survey in the United States to examine dependence using several validated self-report measures in current users of *my*blu ENDS with a range of different nicotine concentrations. Data from young adults are assessed separately from adults due to the current greater regulatory concern regarding young adult ENDS use.

2 | METHODS

2.1 | Recruitment and participants

Data were analysed from three waves of a cross-sectional survey assessing perceptions of the risks, addictiveness and appeal of cigarettes and ENDS, including *my*blu, in a nonprobabilistic nationally representative sample of the United States population. Eligible individuals were young adults (aged 18–24 in Waves 1 and 2 and aged 21–24 in Wave 3) and adults (aged 25 + in all waves) who were enrolled members of an online research panel maintained by Qualtrics, LLC (Provo, UT, USA). Data in this three-wave survey were collected during a period of approximately 4–8 weeks beginning in August 2019, March 2020 and October 2020. Prior to survey conduct and to assure national representation of collected data, quotas were set based on census information for age, sex, education level and region. In each wave of the survey, the overall sample size was set at 2500 young adults and 2500 adults. The survey and all associated documentation were reviewed and approved by the Advarra Institutional

Review Board (IRB; Columbia, MD, USA; Study Number Pro00037947). An invitation email to take part in the survey was sent to potentially eligible participants. Prior to entering the survey, all participants were required to read an on-screen informed consent form and provide electronic consent to participate. Surveys took approximately 25 min to complete, and participants received an IRB-approved financial incentive following survey completion.

Only individuals who at the time of fieldwork were of legal age to purchase tobacco products were allowed to participate. Participants may have been never-smokers or never-ENDS users to take part in the survey; however, only those who had seen or heard of ENDS in general, and of blu or *my*blu ENDS specifically, were allowed to participate. This measure ensured that survey participation did not raise awareness of these products.

2.2 | Survey procedures

Participants who clicked on the link provided in the invitation email were routed to an informed consent form. Individuals who satisfied eligibility criteria, including the age requirement, and gave informed consent to participate began the survey. Efforts were made to ensure that participants did not participate in multiple waves of the survey; however, a small number of participants (138; <1% of the total survey population) completed surveys in two different waves. Data from these participants were not excluded from the analyses.

Based on survey logic, participants were routed to applicable questions based on responses to previous questions. The survey instrument was designed such that all respondents to a question would be asked the next question unless there were specific instructions routing a subgroup of respondents to a different question. For example, only participants who reported being current or ever smokers were asked about their experiences of smoking cigarettes. Participants answered survey questions at their own pace. If a participant did not complete the survey, all data provided up to the point of exit from the survey were deleted.

2.3 | Data quality checks

Manual and automated checks were implemented by Qualtrics to ensure participants who gave low quality or invalid responses were excluded from the perceptions survey dataset. Checks were conducted for straight-lining, geolocation, inattentiveness, speeding, duplicates and bots and were performed independently of the study investigators by Qualtrics.

2.4 | Survey measures

2.4.1 | Demographics

Questions assessed age, sex, region of residence, race and ethnicity.

2.4.2 | Current *my*blu ENDS use

As stated previously, all survey participants were aware of *my*blu ENDS prior to taking part in the survey. To determine whether survey participants were current (past 30-day) *my*blu ENDS users, participants who had indicated prior ENDS use were asked, "Have you ever used a myblu e-cigarette, even once or twice?" If "Yes," participants were asked, "When was the last time you used a myblu e-cigarette, even one or two puffs?" Participants selected one of seven options, with three options ("Earlier today", "Not today but sometime during the past 7 days" and "Not during the past 7 days but sometime during the past 30 days") indicating past 30-day *my*blu use.

2.4.3 | Nicotine concentration of *my*blu ENDS

Participants were asked to indicate the single *my*blu ENDS nicotine concentration they used most often in the past 30 days and selected from eight options (0%, 1%, 1.2%, 2%, 2.4%, 2.5%, 3.6% or 4%). These represented all *my*blu ENDS nicotine concentrations (across both nicotine freebase and nicotine lactate formulations) available at the time of survey conduct. Survey logic prevented participants from selecting illogical responses for *my*blu product type/flavour/nicotine concentrations that did not exist.

2.4.4 | Dependence on *my*blu ENDS

Participants were asked four sequential statements that were modified from the PROMIS Short Form v1.0 Nicotine Dependence Item Banks for Daily and Nondaily Smokers in which smoking-related language was replaced by language relevant to *my*blu ENDS use[37–39] and which were similar to those in the E-cigarette Dependence Scale.[33] The statements were (1) "I find myself reaching for my myblu e-cigarette without thinking about it", (2) "I drop everything to go out and buy a new myblu e-cigarette or more Liquidpods", (3) "I vape my myblu e-cigarette more before going into a situation where vaping is not allowed" and (4) "When I haven't been able to vape my myblu e-cigarette for a few hours, the craving gets intolerable." For each statement, participants indicated that they "Never," "Rarely," "Sometimes," "Often" or "Almost always" took these actions. In addition, participants were asked, "During the past 30 days, have you had a strong craving or felt like you really needed to vape your myblu e-cigarette?"[40] with response options of "Yes" or "No". Further, time to first daily use of *my*blu was assessed using a question modified from the Fagerström Test for Cigarette Dependence,[41,42] which was "How soon after you wake up do you want to vape your myblu e-cigarette?". Response options were "Within 5 minutes", "From 6 to 30 minutes", "From more than 30 minutes to 1 hour", "After more than 1 hour but less than 24 hours" or "I rarely want to use a myblu e-cigarette".

2.5 | Data analysis

This analysis utilised combined datasets from Waves 1, 2 and 3 of a cross-sectional survey. Only participants who were asked the dependence and nicotine concentration questions, per the survey logic outlined above, were included in the analysis. Data collected were weighted based on age, sex, education level, region, race and smoking status. Young adult and adult datasets were weighted independently. Weighting procedures were carried out by Strop Insights (Dallas, TX, USA) using a Random Iterative Method (raking) weighting procedure[43] implemented with WinCross software (The Analytical Group, Inc., Scottsdale, AZ, USA). Analyses were performed with *my*blu ENDS categorised as low (0%, 1% and 1.2%), medium (2%, 2.4% and 2.5%) or high (3.6% and 4%) concentration.

For the modified PROMIS Daily and Nondaily Smokers Short Form 4a Item Bank questions used to assess dependence, each of the four questions had five response options, with scoring ranging from 0 to 4 for each item. Total PROMIS scores were created by summing the item scores, with higher scores indicating greater dependence. The time to first use of a *my*blu ENDS question was scored on a scale of 0 to 4 with higher numbers indicating greater dependence. These scoring approaches allowed us to test the ordered nature of the response options and dependence. Responses to the question regarding a strong craving to vape *my*blu ENDS were analysed as yes/no responses by encoding as 0 for no and 1 for yes.

Analysis of total PROMIS scores was also broken down using a subpopulation of sole *my*blu users. This group was defined as having used *my*blu ENDS in the past 30 days and reporting not having smoked in the past 30 days. Current smoking was assessed from the question "When was the last time you smoked a cigarette, even one or two puffs?"

Statistical analyses were performed on weighted data, and descriptive tables contain raw sample sizes and weighted means, weighted standard error of the mean (SEM) and weighted percentages. Survey-weighted general linear models (GLM) were used to test the relationship of nicotine concentration with the continuous dependent variable of total modified PROMIS scores, taking into account the effect of age group (adults compared with young adults) and consumption (number of days *my*blu was used in the past 30 days) as covariates. When a significant effect of nicotine concentration was observed, pairwise multiple comparison tests (post hoc tests based on Tukey's Honest Significant Difference test) were performed to examine which specific nicotine concentration groups differed significantly from one another.

In addition, survey-weighted logistic regression models were used to test hypotheses of the relationship of nicotine concentration and presence of past 30-day strong cravings, taking into account the effect of age group (adults compared with young adults) and consumption (number of days on which *my*blu was used in the past 30 days). *P* values for these models were obtained from Wald tests. Statistical significance was determined with $p < 0.05$. All analyses were conducted using R (version 3.6.2) with the 'survey' package (version 3.37).

TABLE 1 Participant demographics

Variable	Response	*N* (weighted %) Young adults	*N* (weighted %) Adults
Age	*N*; mean [SEM]	553; 21.9 [0.07]	830; 39.3 [0.37]
Sex	Male	325 (64.5)	573 (66.0)
	Female	220 (34.0)	251 (33.1)
	Transgender	8 (1.5)	6 (0.9)
Region	Northeast	91 (19.5)	205 (24.5)
	South	242 (40.1)	298 (37.7)
	Midwest	120 (20.2)	137 (16.7)
	West	100 (20.1)	190 (21.0)
Hispanic, Latino/Latina, or Spanish origin?	Not of Hispanic, Latino/Latina, or Spanish origin	388 (70.6)	705 (83.2)
	Mexican, Mexican American, or Chicano	79 (13.9)	71 (9.5)
	Puerto Rican	40 (7.0)	19 (2.8)
	Cuban	12 (2.8)	12 (1.6)
	Multiple Hispanic ethnicities	34 (5.8)	23 (2.9)
Race	White	329 (72.2)	680 (74.4)
	Black or African American	128 (15.8)	80 (16.7)
	American Indian or Alaska Native	10 (1.2)	13 (1.0)
	Asian	30 (5.2)	28 (5.6)
	Multiracial	56 (5.5)	29 (2.4)

Note: Data are shown for those participants who reported past 30-day *my*blu use and are included in analyses. Abbreviation: SEM, standard error of the mean.

3 | RESULTS

3.1 | Demographics

Past 30-day *my*blu use was reported by 553 young adults (7.1% of the young adult survey population) and 830 adults (8.6% of the adult survey population). Participant demographics for these 1383 past 30-day *my*blu users whose data were analysed in this study are presented in Table 1. Of the 553 young adult past 30-day *my*blu users, the average age was approximately 22 years and 64.5% were male. For the adults, average age was approximately 39 years and 66% of participants were male. In both age cohorts, participants were predominantly white.

3.2 | *my*blu ENDS users by nicotine concentration

Table 2 presents the number of young adult and adult *my*blu ENDS users by their most commonly used nicotine concentration, with *my*blu nicotine concentrations categorised as low (<2.0%), medium (≥2.0% and ≤2.5%) and high (>2.5%). *my*blu users were spread among the nicotine concentrations, and patterns were similar between the

TABLE 2 *my*blu nicotine concentrations used by age group and *my*blu use status

		All *my*blu users		Sole *my*blu users	
		Young adult *N* (weighted %)	Adult *N* (weighted %)	Young adult *N* (weighted %)	Adult *N* (weighted %)
Low nicotine concentration	0%	19 (4.8)	7 (1.5)	4 (3.5)	2 (2.0)
	1%	12 (2.1)	11 (1.6)	2 (1.0)	3 (2.9)
	1.2%	182 (33.4)	248 (30.3)	58 (34.9)	27 (27.7)
	Total	**213 (40.3)**	**266 (33.4)**	**64 (39.4)**	**32 (32.7)**
Medium nicotine concentration	2%	80 (13.3)	91 (13.2)	21 (13.0)	12 (12.5)
	2.4%	145 (25.3)	290 (31.0)	31 (22.7)	32 (34.8)
	2.5%	49 (8.6)	90 (10.6)	8 (4.9)	7 (6.4)
	Total	**274 (47.2)**	**471 (54.9)**	**60 (40.6)**	**51 (53.6)**
High nicotine concentration	3.6%	34 (6.8)	71 (8.8)	13 (9.0)	9 (10.6)
	4%	32 (5.7)	22 (2.9)	14 (11.0)	3 (3.1)
	Total	**66 (12.5)**	**93 (11.8)**	**27 (20.0)**	**12 (13.7)**

Note: Data are shown both for all *my*blu users and for sole *my*blu users (i.e., those participants who reported current *my*blu use but not current cigarette smoking).

TABLE 3 Modified PROMIS dependence scores for young adults (18–24 years old) and adults (25+ years old) by nicotine concentration

		Young adult						Adult					
		All *my*blu users			Sole *my*blu users			All *my*blu users			Sole *my*blu users		
		N	Mean	SEM	*N*	Mean	SEM	*N*	Mean	SEM	*N*	Mean	SEM
Low nicotine concentration	0%	19	6.25	0.91	4	8.22	1.75	7	6.00	1.90	2	6.32	2.50
	1%	12	5.81	0.98	2	3.00	0.00	11	7.26	1.94	3	1.49	1.15
	1.2%	182	7.36	0.27	58	6.45	0.39	248	8.70	0.26	27	7.83	0.78
	Total	**213**	**7.15**	**0.25**	**64**	**6.51**	**0.38**	**266**	**8.51**	**0.26**	**32**	**7.17**	**0.73**
Medium nicotine concentration	2%	80	7.08	0.40	21	7.23	0.64	91	8.47	0.51	12	9.00	1.06
	2.4%	145	7.74	0.35	31	6.12	0.79	290	8.90	0.26	32	8.13	0.69
	2.5%	49	8.98	0.56	8	8.79	1.29	90	9.40	0.43	7	8.92	1.32
	Total	**274**	**7.78**	**0.24**	**60**	**6.80**	**0.49**	**471**	**8.89**	**0.20**	**51**	**8.43**	**0.52**
High nicotine concentration	3.6%	34	7.35	0.73	13	5.99	1.26	71	9.21	0.52	9	9.04	1.74
	4%	32	8.53	0.77	14	7.89	1.48	22	9.15	0.8	3	7.39	1.53
	Total	**66**	**7.89**	**0.53**	**27**	**7.04**	**0.97**	**93**	**9.20**	**0.44**	**12**	**8.66**	**1.34**

Note: Data are shown for all *my*blu users and sole *my*blu users (i.e., those participants who reported current *my*blu use but not current cigarette smoking).
Abbreviation: SEM, standard error of the mean.

age cohorts; both young adult and adult *my*blu users predominantly reported using low or medium nicotine concentration (X^2 (1) = 0.11, $p = 0.74$). Similar patterns of nicotine concentration use were observed for sole *my*blu users (i.e., those participants who reported current *my*blu use but not current cigarette smoking), with both young adult and adult *my*blu users predominantly reporting using a low or medium nicotine concentration (X^2 (1) = 0.84, $p = 0.36$).

3.3 | Modified PROMIS dependence item bank scores

Summed modified PROMIS dependence bank item scores for an analysis in which *my*blu nicotine concentrations were categorised as low, medium and high are presented in Table 3, while Figure 1 presents data for the total modified PROMIS scores according to nicotine concentration, age group and number of days *my*blu was used in the past 30 days. A GLM revealed a significant effect on PROMIS scores of nicotine concentration groups ($F = 4.07$, $p = 0.02$), age groups (adults had higher total PROMIS scores compared with young adults; $F = 20.01$, $p < 0.001$) and days *my*blu used in the past 30 days (more frequent use was associated with greater total modified PROMIS scores; $F = 30.93$, $p < 0.0001$).

Because a global effect was observed, pairwise multiple comparison tests (post hoc tests based on Tukey's Honest Significant Difference test) were performed to examine which specific groups differed significantly from others. The multiple pairwise comparisons showed no differences; all p values were > 0.05 between nicotine

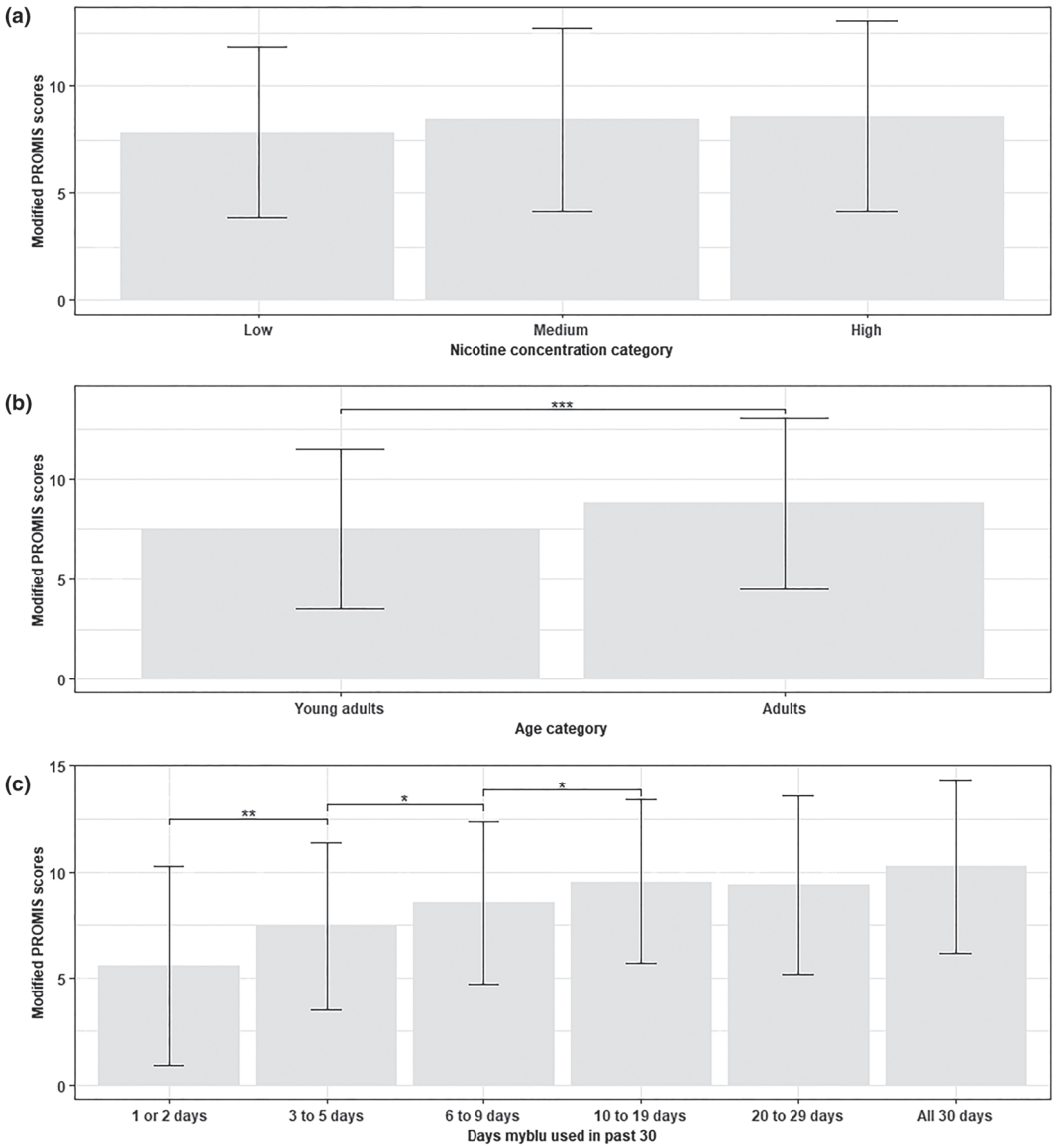

FIGURE 1 Modified PROMIS item bank scores. Data are grouped according to nicotine concentration (a), age group (b) and number of days *my*blu was used in the past 30 days (c). In (a), *my*blu nicotine concentrations were categorised as low (<2.0%), medium (≥2.0% and ≤2.5%) and high (>2.5%). *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$. For clarity, in panel c, asterisks only denote significant differences between two successive groups; for a full breakdown of between-group differences, see supporting information Table S1

concentration groups (low, medium and high). Average PROMIS scores were significantly higher for participants who had used *myblu* ENDS on more than 6 days in the past 30 days compared with 3 to 5 days, and participants who had used *myblu* ENDS on 3 to 5 days had higher average PROMIS scores than those who had used *myblu* ENDS on 1 to 2 days (multiple comparison test based on Tukey contrast; $z = 3.682$, $p = 0.003$).

In a second analysis step, similar evaluations were performed after separating *myblu* users into two groups: sole users (those who currently only use *myblu*) and dual users (those who currently both use *myblu* and smoke cigarettes). The GLM performed on sole users' data revealed no significant relationship among nicotine concentration groups and total modified PROMIS scores ($F = 1.44$, $p = 0.24$). Statistically significant differences in total scores were found for age group ($F = 6.63$, $p = 0.01$) and for number of days on which *myblu* was used in the past 30 days ($F = 7.87$, $p < 0.0001$). On average, total modified PROMIS scores were significantly higher for sole *myblu* use participants who had used *myblu* ENDS on more than 6 days in the past 30 compared with 1 to 2 days use in the past 30 days.

The GLM performed on dual users' data revealed statistically significant differences in total modified PROMIS scores among the nicotine concentration groups ($F = 3.11$, $p = 0.0452$), between age groups ($F = 20.66$, $p < 0.0001$) and among the number of days on which *myblu* was used in the past 30 days ($F = 21.30$, $p < 0.0001$). When performing the multiple pairwise comparisons on nicotine concentration groups (low, medium and high), all p values were > 0.05, meaning that the PROMIS scores were not significantly different between nicotine concentration groups.

3.4 | Craving and time to daily first use measures

Craving scores among users of the different *myblu* ENDS nicotine concentration groups are presented in Figure 2. The logistic regression model revealed a global effect in craving scores of nicotine concentration ($F = 4.09$, $p = 0.02$), age group ($F = 7.32$, $p = 0.00689$) and number of days on which *myblu* was used in the past 30 days ($F = 13.16$, $p < 0.00001$). However, the two-by-two comparison did not show significant differences between nicotine groups; the craving scores among participants using low nicotine concentrations were not significantly different from those using a medium nicotine concentration (odds ratio [OR] = 0.66, 95% confidence interval [CI] [0.42, 1.03], $p = 0.07$) or a high nicotine concentration (OR = 0.95, 95% CI [0.49, 1.82], $p = 0.98$). Craving scores were also not significantly different between young adults and adults (Figure 2; OR = 1.32, 95% CI [0.94, 1.85], $p = 0.103$). For some frequencies of use, there were significant differences in craving scores between those using *myblu* on 1 or 2 days and those using *myblu* more frequently (Figure 2).

Data from assessments of time to daily first use of *myblu* ENDS are presented in Figure 3. An ordered logistic regression model revealed no significant effect of the age group factor (OR = 0.84, $p = 0.13$) or nicotine concentration group factor on the time to first daily use of *myblu* ENDS. Indeed, the time to daily first use of *myblu* ENDS for participants using low nicotine concentrations was not significantly different from those using a medium nicotine concentration (OR = 0.89, 95% CI [0.70, 1.14], $p = 0.35$) or a high nicotine concentration (OR = 0.84, 95% CI [0.57, 1.25], $p = 0.40$).

By comparing times to daily first use of *myblu* ENDS according to the number of days on which *myblu* was used in the past 30 days (Figure 4), our analyses showed that participants who used *myblu* every 1 or 2 days were more likely to use *myblu* within 5 minutes of waking compared with those who used *myblu* with different frequencies (X^2 (20) = 163.42, $p < 0.0001$).

4 | DISCUSSION

The primary finding of our survey data analysis is that self-reported dependence was broadly similar among current *myblu* ENDS users who use different nicotine concentration e-liquids in their *myblu*

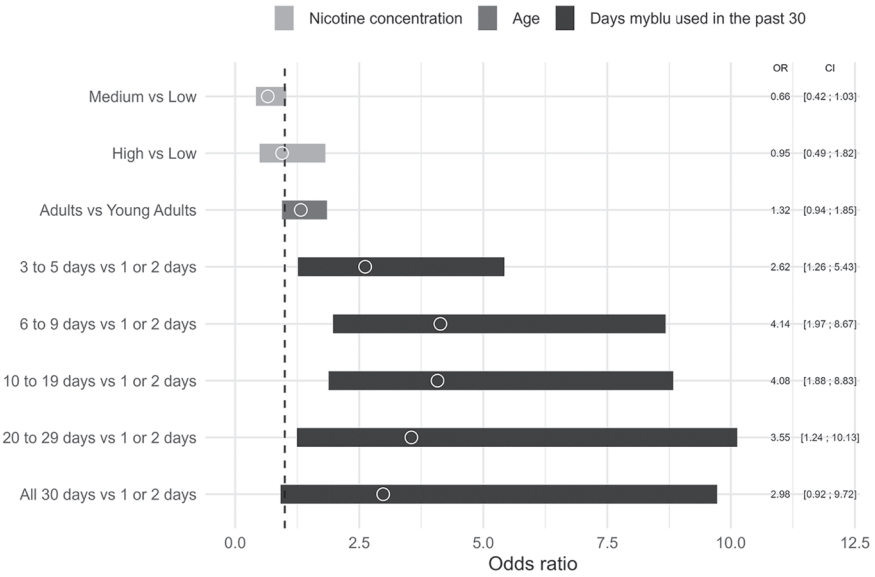

FIGURE 2 Craving scores odds ratios related to age, nicotine level and days *myblu* used in the past 30. Circles represent the odds ratio (OR) of craving scores, and the bars represent the confidence interval. If the confidence interval crosses the dashed line (OR = 1), then the OR is not statistically significant

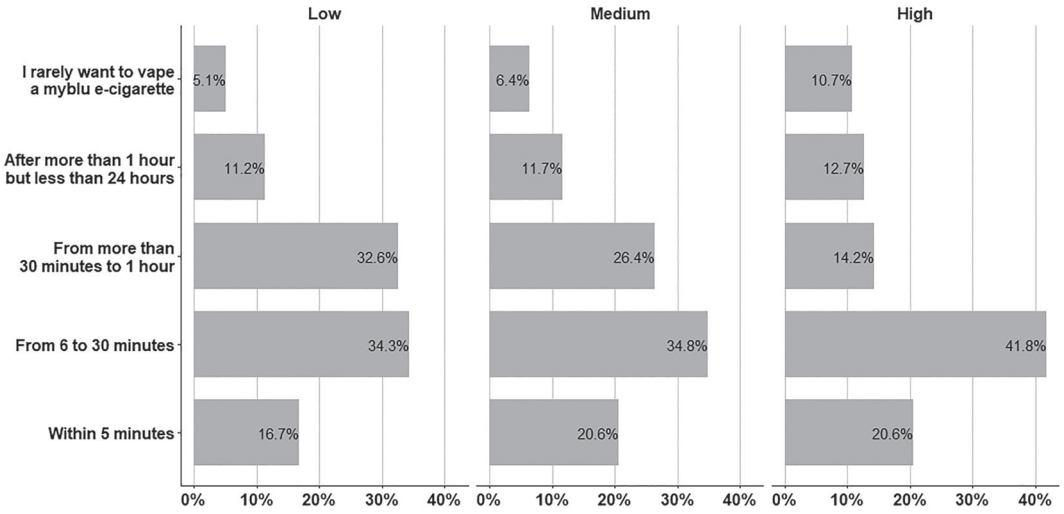

FIGURE 3 Time to daily first use of *my*blu ENDS among users of low, medium and high nicotine concentrations. Data are presented as weighted percentages of participants choosing one of the five response options to answer the question, "How soon after you wake up do you want to vape your *my*blu e-cigarette?" *my*blu nicotine concentrations were categorised as low (<2.0%), medium (≥2.0% and ≤2.5%) and high (>2.5%)

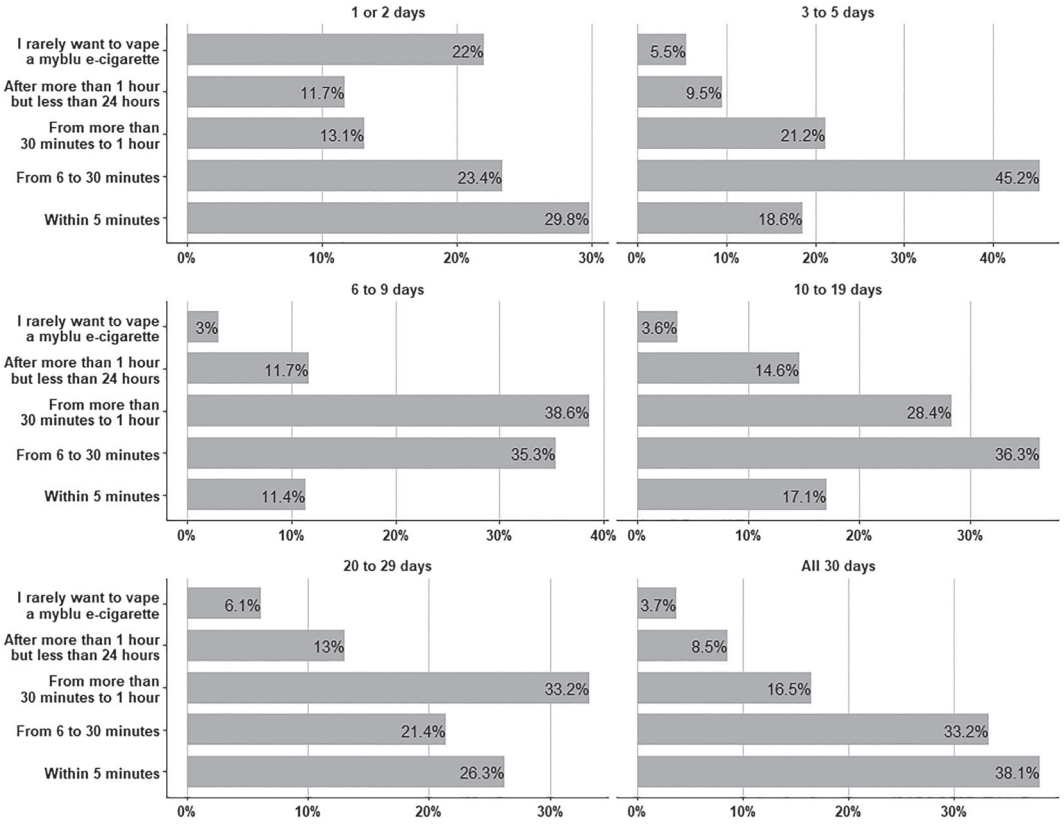

FIGURE 4 Daily first use of *my*blu ENDS by *my*blu days used in the past 30 days. Data are presented as weighted percentages of participants choosing one of the five response options to answer the question, "How soon after you wake up do you want to vape your *my*blu e-cigarette?" and grouped according to their frequency of *my*blu ENDS use in the past 30 days

ENDS. Although a global GLM showed an interaction between *my*blu ENDS nicotine concentration and dependence assessed using modified PROMIS items, pairwise comparisons performed to examine which specific groups differed significantly from others showed no significant differences. Other measures of dependence assessed, which were craving scores and daily time to first use of *my*blu ENDS,

showed no differences between users of high and medium nicotine concentrations compared with users of low nicotine concentrations. Overall, our findings suggest that users of higher nicotine concentrations are no more dependent on *my*blu ENDS than users of lower nicotine concentrations. The strength of these findings is supported by the analysis of data obtained from survey questions from validated tools to assess dependence. Our findings build on those from a recent study that assessed similar measures of dependence (the E-cigarette Dependence Scale, which is comparable to the modified PROMIS statements used in our study) as a function of various factors, including e-liquid nicotine strength.[33] In that study, and as found in our analyses, the use of different e-liquid nicotine concentrations in either disposable or pod-based ENDS was not associated with increased levels of dependence.[33] Additional strengths of our study were the assessment of further dependence measures, including strong cravings and time to first daily use of *my*blu, as well as our use of nationally representative survey samples and examination of a single device type, which mitigates confounding compared with examining across different devices and device types.

An aspect of user behaviour that should be taken into account when considering our findings is the possibility that despite using *my*blu ENDS with different nicotine concentrations, users may be adapting their behaviour and obtaining similar amounts of nicotine regardless of the level of nicotine in the e-liquid, though, of course, this is not applicable to the *my*blu 0% nicotine concentration. A recent clinical study with *my*blu ENDS has demonstrated that using higher nicotine concentrations leads to higher blood nicotine levels,[30] although the relationship between e-liquid nicotine concentration and blood nicotine levels was not linear in this and other studies.[30,44–46] Also of note is that in the aforementioned study,[30] subjects were instructed to take 10 standardised puffs of a 3-second duration and at 30-second intervals. In the real world, users do not puff in such a standardised manner and may titrate their behaviour to obtain different amounts of nicotine from the different nicotine strength *my*blu ENDS, according to their unique individual preferences. Thus, for example, users of lower nicotine concentration *my*blu ENDS may increase their puff duration or frequency to obtain greater amounts of nicotine. This phenomenon of behavioural adaptation has been reported in the literature when ENDS users switch to using different e-liquid nicotine concentrations.[44,47,48] Furthermore, in a clinical study assessing daily nicotine exposure in smokers who switched to using JUUL closed-system pod based ENDS (which are similar to *my*blu ENDS), depending on the flavour used, daily nicotine exposure was either similar in users of different (3% and 5%) e-liquids or different to a much lesser degree than the difference in nicotine concentration.[49] Overall, this leads to the possibility that through adaptation and self-titration, individuals' nicotine intake is not increased linearly with an increase in e-liquid nicotine concentration, and as such, this may mitigate any potential for an increase in dependence when using higher nicotine strength e-liquids.

One finding from this study was a significantly greater level of dependence, in terms of total modified PROMIS item bank and craving scores, in adult users compared with young adult users with the young adults being less dependent. This, however, was not seen with the time to daily first *my*blu ENDS use component of our analyses. Along with the lack of a difference in self-reported dependence in the young adult users of different nicotine concentrations in our survey sample, this similarity in time to daily first *my*blu use potentially alleviates the concern that high nicotine concentration and protonated e-liquids will increase nicotine dependence in adolescents[31] or in the overall population.[32] Furthermore, use of *my*blu ENDS every 1 or 2 days was reported less in young adults than in adults, which also supports the finding of lower dependence in young adults although factors other than dependence, such as opportunities for use and cost, may influence use patterns. Regarding dependence, a variety of different factors such as the sensorial impact may contribute and act as reinforcers for ENDS use, while e-cigarettes do not appear to be as addictive as combustible tobacco cigarettes.[50] This may explain why, in our analyses, e-liquid nicotine concentration alone is not a determinant of dependence.

The results of this study should be interpreted in the context of some limitations. Firstly, our study only assessed a single closed-system ENDS product. Although this is a strength of the study (i.e., examining the impact of nicotine concentration on dependence independent of device type), the extent to which our findings are generalisable to other ENDS within the same class of ENDS products, or ENDS as a whole, is limited. Secondly, the surveys were only conducted in the United States, and as such, findings may not be generalisable to every other region and population in which ENDS products are available. Furthermore, in the United States, ENDS products are available with nicotine concentrations greater than the 4% maximum concentration available for *my*blu ENDS that was assessed in the present study. Given some of those higher nicotine concentration e-liquids are formulated with different nicotine salts, this may modulate nicotine delivery to differing degrees and thus impact dependence. Thirdly, we did not assess *my*blu consumption patterns with any granularity greater than the number of days used in the past month, primarily due to the potential for self-report error in estimating parameters such as numbers of pods used per day or number of puffs taken per day. For cigarettes, at least, a higher number of cigarettes smoked per day is an indicator of greater dependence, but similar *my*blu use factors could not be assessed in our analyses.[51] However, our analyses did include the use of numerous validated measures of dependence as well as time to first use of *my*blu, also a strong indicator of dependence,[51] which is a strength of our approach. Fourthly, we did not examine the interaction of *my*blu e-liquid flavour and nicotine strength on dependence levels. While it has been suggested that flavours may impact ENDS dependence,[52] a recent study has demonstrated that e-liquid flavour did not impact assessments of abuse liability (i.e., dependence potential).[53] Finally, our assessments of dependence were self reported and not objectively confirmed.

5 | CONCLUSIONS

In conclusion, the results of this study suggest that the use of higher *my*blu ENDS nicotine concentration e-liquids was not associated with

greater self-reported dependence, either in young adult or adult current *my*blu users. In addition, young adults reported lower levels of dependence compared with older adults. While our findings add to the ongoing debate regarding factors that contribute to ENDS dependence, further research is necessary to help understand the range of factors, beyond nicotine concentration, which may be associated with dependence on ENDS use.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support of Tanvir Walele and Nveed Chaudhary (formerly of Imperial Brands PLC) in the conduct of these surveys. We also gratefully acknowledge the support of James Gorman, Connor Hennessey-Niland, Tadhg Bogan-Carey and Jasmin Wonik (Qualtrics, LLC) in setting up and running the survey studies and the expert support of Tal Shahar (Strop Insights) in survey programming and data weighting.

AUTHOR CONTRIBUTIONS

IMF developed the survey instruments and undertook QC checks with TH after programming. IMF engaged with Qualtrics to set up and monitor survey recruitment and participation. RGNS performed data analyses and generated data tables. IMF, TH, RGNS and MN interpreted the data and wrote the manuscript. AT, XC, TV, LM, TN and GO'C provided support in manuscript writing and data interpretation. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

IMF is an independent consultant contracted to e-cigarette/tobacco product manufacturers and contract research organisations, including Imperial Brands PLC and LA Clinical Trials, LLC (LACT), to provide scientific support for clinical and behavioural studies and general regulatory support. RGNS was an employee of LACT at the time of survey conduct and analyses. TLH is an independent consultant contracted to LACT to provide analytical and writing support for clinical and behavioural studies. AT, TV, XC, LM, TN and GO'C were employees of Imperial Brands PLC, a company of which Fontem US LLC is a subsidiary, at the time of the study. MN is the President of LACT, which was contracted by Imperial Brands PLC to perform behavioural survey and clinical studies. MN has also contracted to consult with, and conducted behavioural and clinical studies for, other ENDS and smoking cessation medication manufacturers.

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REFERENCES

1. US Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress: A Report of the Surgeon General*. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
2. World Health Organization. *Tobacco*. Accessed 3rd November 2020. https://www.who.int/news-room/fact-sheets/detail/tobacco
3. Gallucci G, Tartarone A, Lerose R, Lalinga AV, Capobianco AM. Cardiovascular risk of smoking and benefits of smoking cessation. *J Thorac Dis*. 2020;12(7):3866-3876.
4. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults - United States, 2000-2015. *MMWR Morb Mortal Wkly Rep*. 2017;65(52):1457-1464.
5. Public Health England. *Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England*. PHE Publications; 2018.
6. Royal College of Physicians. *Nicotine without Smoke. Tobacco Harm Reduction. A Report by the Tobacco Advisory Group of the Royal College of Physicians*. Royal College of Physicians; 2016.
7. Health Canada. *Vaping and quitting smoking*. Accessed 11 May 2022. https://www.canada.ca/en/health-canada/services/smoking-tobacco/vaping/smokers.html
8. New Zealand Ministry of Health. *Position statement on vaping*. https://www.health.govt.nz/our-work/preventative-health-wellness/tobacco-control/vaping-smokefree-environments-and-regulated-products/position-statement-vaping
9. Grabovac I, Oberndorfer M, Fischer J, Wiesinger W, Haider S, Dorner TE. Effectiveness of electronic cigarettes in smoking cessation: A systematic review and meta-analysis. *Nicotine Tob Res*. 2021;23(4):625-634.
10. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380(7):629-637.
11. Hajek P, Phillips-Waller A, Przulj D, et al. E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: The TEC RCT. *Health Technol Assess*. 2019;23(43):1-82.
12. Hartmann-Boyce J, McRobbie H, Butler AR, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2021;9(9):Cd010216.
13. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev*. 2014;(12):Cd010216.
14. Berry KM, Reynolds LM, Collins JM, et al. E-cigarette initiation and associated changes in smoking cessation and reduction: The Population Assessment of Tobacco and Health Study, 2013-2015. *Tob Control*. 2019;28(1):42-49.
15. Kasza KA, Edwards KC, Kimmel HL, et al. Association of e-cigarette use with discontinuation of cigarette smoking among adult smokers who were initially never planning to quit. *JAMA Netw Open*. 2021;4(12):e2140880.
16. Levy DT, Yuan Z, Luo Y, Abrams DB. The relationship of E-cigarette use to cigarette quit attempts and cessation: insights from a large, nationally representative U.S. survey. *Nicotine Tob Res*. 2018;20(8):931-939.
17. Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: Time series analysis of population trends. *Brit Med J*. 2016;354:i4645.
18. Beard E, West R, Michie S, Brown J. Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: A time-series analysis between 2006 and 2017. *Addiction*. 2020;115(5):961-974.
19. Giovenco DP, Delnevo CD. Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers. *Addict Behav*. 2018;76:129-134.
20. Pierce JP, Benmarhnia T, Chen R, et al. Role of e-cigarettes and pharmacotherapy during attempts to quit cigarette smoking: The PATH Study 2013-16. *PLoS ONE*. 2020;15(9):e0237938.
21. Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: Evidence from US current population surveys. *BMJ*. 2017;358:j3262.

22. Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob Control*. 2018; 27(1):18-25.
23. Mendez D, Warner KE. A magic bullet? The potential impact of e-cigarettes on the toll of cigarette smoking. *Nicotine Tob Res*. 2020; 23(4):654-661.
24. Hajek P, Pittaccio K, Pesola F, Myers Smith K, Phillips-Waller A, Przulj D. Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction*. 2020;115(6): 1141-1148.
25. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2012;(11): PMID: Cd000146.
26. Food and Drug Administration. *PMTA Coversheet: Technical Project Lead Review (TPL)*. Accessed 23rd September 2020. https://www.fda.gov/media/124247/download
27. Fearon IM, Eldridge AC, Gale N, McEwan M, Stiles MF, Round EK. Nicotine pharmacokinetics of electronic cigarettes: A review of the literature. *Regul Toxicol Pharmacol*. 2018;100:25-34.
28. Jackson A, Grobman B, Krishnan-Sarin S. Recent findings in the pharmacology of inhaled nicotine: Preclinical and clinical in vivo studies. *Neuropharmacology*. 2020;176:108218.
29. Maloney S, Eversole A, Crabtree M, Soule E, Eissenberg T, Breland A. Acute effects of JUUL and IQOS in cigarette smokers. *Tob Control*. 2020. https://doi.org/10.1136/tobaccocontrol-2019-055475
30. O'Connell G, Pritchard JD, Prue C, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med*. 2019;14(6):853-861.
31. Voos N, Goniewicz ML, Eissenberg T. What is the nicotine delivery profile of electronic cigarettes? *Expert Opin Drug Deliv*. 2019;16(11): 1193-1203.
32. Cahn Z, Drope J, Douglas CE, et al. Applying the population health standard to the regulation of electronic nicotine delivery systems. *Nicotine Tob Res*. 2021;23(5):780-789.
33. Do EK, O'Connor K, Perks SN, et al. E-cigarette device and liquid characteristics and E-cigarette dependence: A pilot study of pod-based and disposable E-cigarette users. *Addict Behav*. 2022;124: 107117.
34. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: What are they and what do they do? *Ann N Y Acad Sci*. 2017;1394(1):5-30.
35. El-Hellani A, Salman R, El-Hage R, et al. Nicotine and carbonyl emissions from popular electronic cigarette products: correlation to liquid composition and design characteristics. *Nicotine Tob Res*. 2018;20(2): 215-223.
36. Kosmider L, Spindle TR, Gawron M, Sobczak A, Goniewicz ML. Nicotine emissions from electronic cigarettes: Individual and interactive effects of propylene glycol to vegetable glycerin composition and device power output. *Food Chem Toxicol*. 2018;115:302-305.
37. RAND Corporation. *PROMIS Short Form v1.0 – Smoking: Nicotine Dependence for Daily and Nondaily Smokers 4a*. Accessed 22 September 2020. https://www.rand.org/content/dam/rand/www/external/health/projects/promis/short-forms/nicotine-dependence-4a.pdf
38. Shadel WG, Edelen MO, Tucker JS, Stucky BD, Hansen M, Cai L. Development of the PROMIS nicotine dependence item banks. *Nicotine Tob Res*. 2014;16(Suppl 3):S190-S201.
39. Morean ME, Krishnan-Sarin S, Sussman S, et al. Psychometric evaluation of the E-cigarette dependence scale. *Nicotine Tob Res*. 2019; 21(11):1556-1564.
40. Centers for Disease Control and Prevention. *2019 National Youth Tobacco Survey (NYTS) Questionnaire*. Accessed 22 September 2020. https://www.cdc.gov/tobacco/data_statistics/surveys/nyts/data/index.html
41. Fagerström K. Determinants of tobacco use and renaming the FTND to the Fagerström Test for Cigarette Dependence. *Nicotine Tob Res*. 2012;14(1):75-78.
42. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: A revision of the fagerström tolerance questionnaire. *Br J Addict*. 1991;86(9): 1119-1127.
43. Weighting ST, Results S. *J Mark Res Society*. 1986;28:269-284.
44. Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: Blood nicotine delivery and subjective effects. *Psychopharmacology (Berl)*. 2016;233(15-16): 2933-2941.
45. Stiles MF, Campbell LR, Graff DW, Jones BA, Fant RV, Henningfield JE. Pharmacodynamic and pharmacokinetic assessment of electronic cigarettes, combustible cigarettes, and nicotine gum: Implications for abuse liability. *Psychopharmacology (Berl)*. 2017; 234(17):2643-2655.
46. Stiles MF, Campbell LR, Jin T, Graff DW, Fant RV, Henningfield JE. Assessment of the abuse liability of three menthol Vuse Solo electronic cigarettes relative to combustible cigarettes and nicotine gum. *Psychopharmacology (Berl)*. 2018;235(7):2077-2086.
47. Dawkins L, Cox S, Goniewicz M, et al. 'Real-world' compensatory behaviour with low nicotine concentration e-liquid: Subjective effects and nicotine, acrolein and formaldehyde exposure. *Addiction*. 2018; 113(10):1874-1882.
48. Kosmider L, Kimber CF, Kurek J, Corcoran O, Dawkins LE. Compensatory Puffing With Lower Nicotine Concentration E-liquids Increases Carbonyl Exposure in E-cigarette Aerosols. *Nicotine Tob Res*. 2018; 20(8):998-1003.
49. Cohen G, Goldenson NI, Bailey PC, Chan S, Shiffman S. Changes in biomarkers of cigarette smoke exposure After 6 days of switching exclusively or partially to use of the juul system with two nicotine concentrations: A Randomized Controlled Confinement Study in Adult Smokers. *Nicotine Tob Res*. 2021;23(12):2153-2161.
50. West R, Cox S. The 1988 US Surgeon General's report Nicotine Addiction: How well has it stood up to three more decades of research? *Addiction*. 2021. https://doi.org/10.1111/add.15754
51. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: Using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict*. 1989;84(7):791-799.
52. DeVito EE, Krishnan-Sarin S. E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure. *Curr Neuropharmacol*. 2018;16(4):438-459.
53. Goldenson NI, Buchhalter AR, Augustson EM, Rubinstein ML, Henningfield JE. Abuse liability assessment of the JUUL system in four flavors relative to combustible cigarette, nicotine gum and a comparator electronic nicotine delivery system among adult smokers. *Drug Alcohol Depend*. 2020;217(4):108395.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Fearon IM, Seltzer RGN, Houser TL, et al. Examination of the impact of *my*blu electronic nicotine delivery system e-liquid nicotine strength on self-reported measures of dependence. *Drug Test Anal*. 2022;1-11. doi:10.1002/dta.3335