



## Full length article

# The interaction of sociodemographic risk factors and measures of nicotine dependence in predicting maternal smoking during pregnancy



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## ABSTRACT

**Background:** Understanding differences in nicotine dependence assessments' ability to predict smoking cessation is complicated by variation in quit attempt contexts. Pregnancy reduces this variation, as each pregnant smoker receives the same strong cessation incentive. Cigarette smoking during pregnancy (SDP) provides a powerful paradigm for analyzing the interplay between nicotine dependence measures and sociodemographics in predicting cessation failure.

**Methods:** Data from a female twin cohort (median birth year 1980), assessed in teens and early twenties, were merged with birth records to identify those with smoking history who experienced childbirth (N = 1657 births, N = 763 mothers). Logistic regression predicting SDP, as a function of birth record sociodemographic variables, generated a sociodemographic risk-score. Further analysis incorporated the risk-score with data from research interviews on DSM-IV-Nicotine Dependence symptom count, Heaviness of Smoking Index.

**Results:** Low maternal educational level, younger age at childbirth, and being unmarried all contributed risk for SDP. In addition to sociodemographic risk-score, the best predictors of SDP included HSI-score (OR:1.51), their two-way interaction (OR:0.39; reduced impact of dependence at intermediate-high sociodemographic risk), history of  $\geq$  two failed quit attempts (OR:1.38), and a dummy variable for prior pregnancy at time of assessment (OR:1.82). DSM-IV-Nicotine Dependence symptoms underperformed the Heaviness of Smoking Index and did not improve prediction when added to the best model.

**Conclusions:** The 2-item Heaviness of Smoking Index measure and report of  $\geq$  two failed quit attempts performed best for predicting SDP. The contribution of either nicotine dependence measure to SDP risk was diminished at increased levels of sociodemographic risk.

## 1. Introduction

While risk and protective factors for onset of substance use and problem use are well-described, determinants of successful recovery and cessation are less clear, particularly given variability in the contexts of quit attempts (e.g., proximal stressors, major life-changing events, self-efficacy for cessation; Bolman et al., 2018; Koslovsky et al., 2018; Volz et al., 2014). Using outcomes of a large number of users under similar conditions enables inference about risk- and protective-mechanisms in addiction persistence and desistance. Cigarette smoking

during pregnancy is a useful model for identifying predictors of cessation failure because many smokers experience a common, strong incentive for cessation: pregnancy, or the anticipation of pregnancy (Practice Committee of the American Society for Reproductive Medicine, 2018).

Smoking during pregnancy prevalence ranges from 8.4%–16.5%, depending whether it is reported from surveillance data or a U.S. nationally-representative sample (Brown et al., 2016; Curtin and Matthews, 2016). These rates exceed the Healthy People 2020 goal of reduction to 1.4% (U.S. Department of Health and Human Services).

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Smoking during pregnancy has been associated with newborn outcomes such as low birth weight and premature birth (Cnattingius, 2004; Dietz et al., 2010) and more distal outcomes such as chronic respiratory issues (McEvoy and Spindel, 2017; Tager et al., 1983), structural brain changes (El Marroun et al., 2016), and psychiatric phenotypes, especially hyperactive/impulsive symptoms (Knopik et al., 2016; for review see Scherman et al., 2018). Smoking during pregnancy provides a powerful model system for examining the interplay of biological factors, such as inherited differences in nicotine dependence vulnerability (for review see Sharp and Chen, 2018), and sociodemographic factors (for review see Chamberlain et al., 2017; Riaz et al., 2018). Given low rates of smoking cessation in pregnancy and high rates of post-partum relapse (Cnattingius, 2004), identifying early predictors of future smoking during pregnancy risk will improve early screening and intervention.

A measure's predictive utility for smoking during pregnancy is influenced by how nicotine dependence is assessed. The nicotine dependence construct aims to assess problems associated with nicotine use that have individual and societal impact (IARC Handbooks of Cancer Prevention, 2008; Piper et al., 2006). Nicotine dependence measures commonly assess themes of difficulty quitting, experiencing problems related to use, and heaviness of use. There are global assessments, such as the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) and the Diagnostic and Statistical Manual of Mental Disorders Nicotine Dependence criteria (DSM; American Psychiatric Association (APA, 1994), now assessed as Tobacco Use Disorder in the most recent DSM-5 (American Psychiatric Association (APA, 2013), and more focused measures for identifying and defining subgroups of smokers (Piper et al., 2008), including the Nicotine Dependence Syndrome Scale (Shiffman et al., 2004) and Wisconsin Inventory of Smoking Dependence Motives (Piper et al., 2004). The six-item FTND and related Heaviness of Smoking Index (HSI; Heatherton et al., 1989), containing two FTND items, measure physical nicotine dependence. Both have been shown to predict smoking cessation outcomes (Baker et al., 2012). The DSM-IV assessment of nicotine dependence uses a medical model framework to identify “a maladaptive pattern of nicotine use, leading to clinically significant impairment or distress” (American Psychiatric Association (APA, 2000) and has modest ability to predict smoking cessation outcomes, yet generally underperforms other measures (Baker et al., 2012).

Understanding the relationship between nicotine dependence, sociodemographic factors, and risk of smoking during pregnancy is arguably best achieved prospectively, since failure of smoking cessation during pregnancy may impact a participant's evaluation of own nicotine dependence (e.g., greater likelihood of endorsement of nicotine dependence). In this report, we use data from a large female twin cohort, with many participants assessed prior to first pregnancy, in tandem with data from state birth records, to analyze the interplay of sociodemographic characteristics at the time of childbirth, and research assessments of nicotine dependence, in predicting smoking during pregnancy as recorded on the birth record.

## 2. Methods and materials

### 2.1. Sample

Analyses used Missouri Adolescent Female Twin Study (MOAFTS) data, described previously (Heath et al., 2002). Briefly, a like-sex female twin pair cohort (monozygotic and dizygotic), born July 1st 1975–June 30th 1985, was ascertained from Missouri birth records. Parents (“Generation 1” – G1) and their twin daughters (“Generation 2” – G2) were recruited using a cohort-sequential design for a prospective study initially focused on the predictors and long-term outcomes of alcohol misuse in adolescent girls. Data for this report comes from the first major follow-up telephone diagnostic interview of the original target sample of twins, after G2 age 18 (G2 median age 22, range 18–28,

N = 3787 twins, 81.7% of the total cohort identified from birth records, 14% African American; Sartor et al., 2013). Informed consent was obtained. Study procedures were approved by the Washington University Institutional Review Board and comply with the Declaration of Helsinki. State birth record data from 1993 to 2016 were used to identify children (“Generation 3” – G3) that were born to MOAFTS twins (G2). The final sample included G2 participants who were regular smokers (defined in 2.2.1), had given birth and participated in the follow-up interview: a total of 1657 births to 763 white participants and 177 births to 65 African American participants were identified. Rates of smoking during pregnancy in African American mothers are lower (Mumford et al., 2014), and smoking trajectories for smoking during pregnancy differ between white and African American mothers (De Genna et al., 2017). Due to these differences, we had insufficient power to conduct separate analyses in African American mothers. We find it inappropriate to collapse these samples by race, given the limited sociodemographic overlap of white and African American twins, which would lead to predictions for cells with no data (Imbens and Rubin, 2015). Thus, we present analyses only for white mothers.

### 2.2. Measures

Follow-up interview assessments of the G2 twins were based on the Semi-Structured Assessment of the Genetics of Alcoholism (Bucholz et al., 1994) adapted for telephone interview. This measure is an extensively-validated semi-structured interview initially developed for the Collaborative Study on the Genetics of Alcoholism (Begleiter et al., 1995; Bucholz et al., 1994; Hesselbrock et al., 1999). The smoking section of the interview is based on items from the Composite International Diagnostic Interview (World Health Organization (WHO, 1997).

#### 2.2.1. Nicotine dependence measures from the research data

We adopted the commonly used definition of regular smoking recommended by the CDC: ever smoking  $\geq 100$  lifetime cigarettes. This definition includes ‘current’ and ‘former’ smokers at time of research interview, who are the pool of people at risk for smoking during pregnancy. The tobacco use module included assessment of the Heaviness of Smoking Index (HSI) and criteria for DSM-IV Nicotine dependence diagnosis. The HSI (Heatherton et al., 1991, 1989) is a widely-used two-item measure to assess nicotine dependence containing two-items: *Time-to-First-Cigarette* and *Cigarettes-(smoked)-Per-Day*. The variables included in the present analyses include: 1) Total HSI score, as a sum of the points for each item ranging from 0 to 7, with higher numbers indicating more severe nicotine dependence, coded into a six-level ordinal variable corresponding to HSI scores of: 0, 1, 2, 3, 4–5, 6–7; 2) individual *Time-to-First-Cigarette* item and 3) individual *Cigarettes-Per-Day* item, coded as above.

DSM-IV-Nicotine Dependence was assessed via structured questions to capture the following items: *tolerance*, *great deal of time using important activities given up*, *smoking more than intended*, *difficulty quitting* (experienced  $\geq 2$  lifetime failed quit attempts) or *persistent desire to quit*, *withdrawal syndrome* (experienced  $\geq 4$  symptoms within 24 h of last cigarette use), and *use despite experiencing physical or emotional health problems related to smoking*. The DSM-based variables used in the present analyses include: 1) A symptom count variable characterized as a six-level ordinal variable corresponding to 0, 1, 2, 3, 4,  $\geq 5$  symptoms; ND-sx, 2) a dichotomous variable indicating a DSM-IV-Nicotine Dependence diagnosis, by endorsing three or more symptoms; ND-dx and 3) individual symptom level data. To reflect the DSM criterion, the *two or more failed quit attempts* item was combined with *persistent desire to quit* for the total DSM symptom score, but these two symptoms were analyzed separately for the individual symptom level analyses. For more detail on coding of Nicotine Dependence measures, see *Supplemental Methods*.

**Table 1**  
Maternal sociodemographic characteristics at childbirth recorded on birth record.

Smoking Status at Follow Up Interview	Never Smokers		Regular Smokers, Never SDP <sup>a</sup>		Regular Smokers, SDP for $\geq 1$ birth <sup>a</sup>	
	N	%	N	%	N	%
<b>Maternal Age</b>						
Under 18	28	1.41	25	3.26	61	6.79
18–19	90	4.54	44	5.74	111	12.35
20–23	291	14.69	177	23.11	276	30.70
24–26	426	21.50	130	16.97	172	19.13
27–30 (reference)	667	33.67	209	27.28	173	19.24
31 or greater	479	24.18	181	23.63	106	11.79
<b>Maternal Marital Status</b>						
Unmarried, Partner Unnamed	107	5.40	59	7.70	185	20.58
Unmarried, Partner Named	281	14.18	173	22.58	342	38.04
Married, Partner Named (reference) <sup>b</sup>	1590	80.26	532	69.45	349	38.82
Married, Partner Unnamed <sup>b</sup>	3	0.15	2	0.26	23	2.56
<b>Years Education Completed</b>						
Less than 8 years	8	0.40	12	1.57	42	4.75
9–12 years (reference)	495	25.03	313	40.86	617	69.80
13–15 years	501	25.33	210	27.42	193	21.83
16 years	651	32.91	143	18.67	23	2.60
17 years	323	16.33	88	11.49	9	1.02

Sample size, N, refers to number of births, since maternal characteristics could change between births.

<sup>a</sup> “Regular Smoker” status (100+ cigarettes lifetime) determined at time of research follow-up interview, median age 22. SDP status determined across all birth records to a given mother ascertained from birth record data.

<sup>b</sup> Since under state law a woman married at any stage during pregnancy is recorded as married, this group could include women who had already divorced their partner.

### 2.2.2. Pregnancy data

Given that the experience of difficulty quitting during pregnancy could influence a participant’s endorsement of nicotine dependence symptoms, we compared prospective with retrospective prediction. Prospective prediction occurred when nicotine dependence items were assessed prior to the participant ever experiencing pregnancy. Retrospective prediction occurred when nicotine dependence assessment occurred after a participant experienced their first pregnancy. There was 98.6% concordance between self-report pregnancy history and state birth record data on childbirth. In cases of discordance, birth record data superseded self-report.

### 2.2.3. Birth record data

Missouri birth records from 1993 to 2016 including identifiers were obtained with permission from the state Department of Health and Senior Services and linked at the individual level for all in-state births of G3 children to G2 MOAFTS participants. Sociodemographic variables from the birth record were recoded when necessary for consistency across years and used to create the sociodemographic risk score (SRS), see 2.3.1. Variables used for the SRS: maternal age, maternal highest educational attainment, marital status, parity (yes/no indicating first born child, due to lower rates of smoking during pregnancy for first-pregnancy compared with subsequent-pregnancy; Meernik and Goldstein, 2015), and a dummy variable to represent a coding change initiated by the CDC, implemented in 2010 (2010-onwards: smoking during pregnancy by trimester; 1993-2009: dichotomous smoking at any time during pregnancy). The primary outcome is thus smoking during pregnancy as recorded on the birth record, with cases for 2010-onwards reflecting smoking during pregnancy beyond the first trimester. For more details about birth record variables and our coding of these variables, see *Supplementary Methods*.

### 2.3. Data analysis

Descriptive statistics were calculated with SAS Version 9.2 (SAS Institute Inc., Cary, NC). Descriptive statistics for sample characteristics were calculated based on smoking status at time of research interview:

never smokers (reported never smoking or smoking < 100 lifetime cigarettes), regular smokers ( $\geq 100$  lifetime cigarettes) with no reports of smoking during pregnancy on the birth record, and regular smokers with  $\geq 1$  report of smoking during pregnancy on the birth record. Descriptive statistics for smoking variables were calculated on both groups of smokers. Generalizability of findings from twin cohort research data was assessed by comparing MOAFTS participants versus other non-twin mothers, who were born in state during the same birth years as the MOAFTS participants (1975–1985), on key socio-demographic variables.

#### 2.3.1. Generation of sociodemographic risk score (SRS)

Logistic regression analyses predicting smoking during pregnancy from the birth record as the primary outcome were calculated using STATA Version 15.1 (StataCorp, College Station, TX). All births were included; thus, the same mother could be represented on multiple records. To generate the SRS, predicted probabilities of smoking during pregnancy were estimated using logistic regression with the birth record variables described in 2.2.3., adjusted for clustered samples using the STATA *robust cluster* command. SRS was then sextiled for use in subsequent analyses to protect confidentiality, a requirement for working with state birth record data.

#### 2.3.2. Analyses using SRS, HSI, DSM-ND

To identify which smoking variables had best utility for predicting smoking during pregnancy, individual adjusted logistic regressions were performed predicting smoking during pregnancy from smoking characteristic separately: HSI score, HSI individual items; DSM-based ND-sx (symptom count), ND-dx (endorsement of  $\geq 3$  symptoms), and individual DSM-IV-Nicotine Dependence items. The HSI analyses were adjusted for SRS. The DSM-IV-Nicotine Dependence analyses were adjusted for SRS and individual HSI items to evaluate their ability to improve prediction of smoking during pregnancy beyond HSI and sociodemographic risk. Additional logistic regression models, stratified by prospective (no pregnancy by research interview) versus retrospective (experienced at least one pregnancy by time of research interview) assessment of nicotine dependence relative to first pregnancy,

investigated the interaction between SRS and smoking characteristic (HSI, ND-sx) on predicting smoking during pregnancy risk.

### 3. Results

#### 3.1. Sample characteristics

Sociodemographic characteristics of never-smokers, regular smokers with no report of smoking during pregnancy, and regular smokers with report of smoking during at least one pregnancy (“pregnancy smokers”) are summarized in Table 1. These show the expected differences: Compared to never smokers, both groups of smokers were younger at childbirth, had completed fewer years of education, and were more likely to be unmarried, with these differences more pronounced for pregnancy smokers. For both groups of regular smokers, the endorsement rate for nicotine dependence symptoms at interview is shown in Table 2. Across all variables except difficulty quitting/persistent desire to quit, higher endorsement rates were seen among pregnancy smokers.

Supplementary Table 1 presents additional birth record sample characteristics for mother and child at time of childbirth: Pregnancy smokers were, on average, younger at first childbirth. Sociodemographic variables at childbirth between MOAFTS participants and all other mothers, themselves born in state 1975–1985, show minimal differences (Spearman  $\rho$ s < |0.02|; Supplementary Table 2). For participants who experienced first pregnancy after research interview (prospective nicotine dependence assessment), children were born 7.0 years after research interview (N = 593 births). For participants who had at least one pregnancy by time of research interview (retrospective nicotine dependence assessment), children were born on average 2.9 years before research interview (N = 577 births) and 5.3 years after research interview (N = 490 births).

#### 3.2. Sociodemographic predictors of smoking during pregnancy risk

The results of fitting a multiple logistic regression predicting smoking during pregnancy are summarized in Table 3. Smoking during pregnancy risk is reduced in those younger than age 18 at childbirth and those who completed more years of education, with the protective effect of education particularly strong. Compared to the married, partner named reference group, smoking during pregnancy risk is elevated both by being unmarried during pregnancy and having an unnamed reproductive partner. The control variable correcting for the effects of the CDC coding change was non-significant. In a separate analysis including a dummy variable for whether first childbirth occurred before or after research interview, an increased risk in those interviewed after their first birth was noted (OR:1.82, 95% CI: [1.33, 2.49]). When comparing rates of smoking during pregnancy by birth year between the retrospective and prospective analyses, we observe higher rates for each birth year in those who had first pregnancy by research assessment (unpublished data, available upon request).

#### 3.3. Joint effects of sociodemographic risk and individual nicotine dependence measures

Spearman correlations among the nicotine dependence variables were low to modest, ranging from 0.05 to 0.34 (Supplementary Table 3). Table 4 summarizes the association between HSI measures obtained at research interview and smoking during pregnancy, controlling for sociodemographic variables (Model 1a: HSI-total score; Model 1b: HSI *time-to-first-cigarette*; Model 1c: HSI *cigarettes-per-day*); and then between DSM-IV-Nicotine Dependence measures and smoking during pregnancy, controlling for both SRS and HSI items (Model 2a: ND-sx count; Model 2b: ND-dx; Model 3, individual nicotine dependence symptoms, entered separately). The HSI items improve prediction of smoking during pregnancy risk, but the DSM symptom count

**Table 2**  
Maternal smoking characteristics at research interview.

Smoking Status at Follow Up Interview	Regular Smokers, Never SDP <sup>a</sup>	%	Regular Smokers, SDP for $\geq 1$ birth <sup>a</sup>	%
<b>Heaviness of Smoking Index (HSI) Score</b>				
0	N = 391	86	N = 369	11
1		21.99		2.98
2		18.16		8.67
3		16.62		10.57
4		13.55		12.47
5		9.46		14.63
6		8.44		15.72
7		8.18		13.01
		3.58		21.95
<b>HSI: Cigarettes Per Day</b>				
1–5	N = 391	108	N = 369	19
6–10		27.62		5.15
10–15		27.88		23.04
16–19		17.90		22.22
20+		12.28		13.82
		14.32		35.77
<b>HSI: Time to First Cigarette</b>				
> 60 minutes	N = 394	203	N = 369	69
31–60 minutes		51.52		18.70
6–30 minutes		17.77		15.18
$\leq 5$ minutes		22.08		29.54
		8.63		36.59
<b>DSM IV Nicotine Dependence</b>				
Symptom Count	N = 394		N = 369	
0		38		21
1		95		41
2		94		87
3		62		66
4		61		65
$\geq 5$		44		89
Diagnosis ( $\geq 3$ Symptoms)		158		207
		40.10		56.10
<b>DSM IV Nicotine Dependence Symptoms</b>				
Tolerance	N = 391	150	N = 369	224
Great Deal of Time Using		38.07		60.70
Important Activities Given Up		23.10		28.46
Smoke More Than Intended		4.82		8.67
Difficulty Quitting/ Persistent Desire To Quit		168		211
$\geq$ Two Failed Quit Attempts		321		304
Withdrawal Syndrome ( $\geq 4$ Symptoms)		171		222
Use Despite Physical/ Emotional Problems		134		166
		34.01		44.99
		17.01		30.89

Sample size N refers to number of mothers with history of regular smoking who have given birth in state.

<sup>a</sup> “Regular Smoker” status (100+ cigarettes lifetime) determined at time of research follow-up interview, median age 22. SDP status determined across all birth records to a given mother ascertained from birth record data.

(OR:1.02, 95% CI [0.92–1.13]) and binary diagnostic measures (OR:1.00, 95% CI [0.74–1.35]) show a striking lack of further improvement in prediction. Only a single DSM-based measure, reporting two or more unsuccessful efforts to quit smoking, improves prediction.<sup>1</sup> Spearman correlation between HSI items was moderate (0.54), while

<sup>1</sup> Given that past experience of failed quit attempts during pregnancy might influence responding to this item, we ran an additional model predicting smoking during pregnancy including a dichotomous variable indicating whether a participant experienced first pregnancy by time of follow-up interview, the symptom of experiencing two or more failed quit attempts, and their two-way interaction, adjusted for SRS and two HSI items, and observed a significant interaction term (OR: 1.97, 95% CI: [1.07, 3.60]), confirming our concern.

**Table 3**  
Prediction of smoking during pregnancy using sociodemographic variables at time of childbirth analyzed with logistic regression.

Maternal Age (years)	Odds Ratio	95% CI	
Under 18	0.46	0.23	0.90
18–19	0.80	0.49	1.30
20–23	0.82	0.56	1.21
24–26	0.94	0.66	1.34
27–30 (reference)	–	–	–
31 or greater	0.85	0.56	1.28
<b>Maternal Marital Status</b>			
Married, Partner Named (reference)	–	–	–
Married, Partner Unnamed	6.74	2.80	16.25
Unmarried, Partner Named	2.14	1.58	2.90
Unmarried, Partner Unnamed	2.26	1.56	3.27
<b>Maternal Educational Attainment (years)</b>			
Less than 8	1.74	0.66	4.56
9–12 (reference)	–	–	–
13–15	0.58	0.42	0.79
16	0.15	0.08	0.27
17	0.11	0.04	0.26
<b>CDC Coding Change (dummy variable)</b>	1.09	0.71	1.68
<b>First Born Child (yes/no)</b>	0.79	0.62	1.00

**Table 4**  
Comparison of the ability of smoking characteristics from research data to predict smoking during pregnancy beyond sociodemographic variables at time of childbirth analyzed with logistic regression.

Model		Odds Ratio	95% CI	
<b>1</b>	<b>Heaviness of Smoking Index<sup>a</sup></b>			
1a	Heaviness of Smoking Index Score	<b>1.51</b>	<b>1.36</b>	<b>1.66</b>
1b	Time To First Cigarette			
	≥ 60 minutes (reference)	–	–	–
	31–60 minutes	<b>2.39</b>	<b>1.51</b>	<b>3.78</b>
	6–30 minutes	<b>2.72</b>	<b>1.84</b>	<b>4.03</b>
	≤5 minutes	<b>6.05</b>	<b>3.87</b>	<b>9.46</b>
1c	Cigarettes Per Day			
	1–5 (reference)	–	–	–
	6–10	<b>3.27</b>	<b>1.83</b>	<b>5.85</b>
	11–15	<b>4.18</b>	<b>2.31</b>	<b>7.57</b>
	16–20	<b>4.83</b>	<b>2.51</b>	<b>9.30</b>
	≥21	<b>7.73</b>	<b>4.29</b>	<b>13.92</b>
<b>2</b>	<b>DSM IV Nicotine Dependence<sup>b</sup></b>			
2a	Symptom Count	1.02	0.92	1.13
2b	Diagnosis (≥3 Symptoms)	1.00	0.74	1.35
<b>3</b>	<b>DSM IV Nicotine Dependence Symptoms</b>			
	Tolerance	1.01	0.72	1.43
	Great Deal of Time Using	0.86	0.61	1.23
	Important Activities Given Up	0.92	0.54	1.54
	Smoke More Than Intended	1.36	1.00	1.84
	Difficulty Quitting/Persistent Desire To Quit	1.04	0.72	1.50
	≥ Two Failed Quit Attempts	<b>1.38</b>	<b>1.02</b>	<b>1.86</b>
	Withdrawal Syndrome (≥ 4 Symptoms)	0.80	0.59	1.11
	Use Despite Physical/Emotional Problems	1.03	0.75	1.42

<sup>a</sup> Heaviness of Smoking Index analyses were run as three separate logistic regression models adjusted for sociodemographic risk score at time of childbirth ascertained from birth record data.

<sup>b</sup> DSM-IV-Nicotine Dependence analyses were run as separate logistic regression models per variable listed, adjusted for sociodemographic risk score and the individual Heaviness of Smoking Index Items (Time to First Cigarette and Cigarettes Per Day).

those between HSI items and the ≥2 failed quit attempts item were low: *time-to-first-cigarette* and ≥2 failed quit attempts (0.21) and *cigarettes-per-day* and ≥2 failed quit attempts (0.15).

Fig. 1 summarizes predicted probability of smoking during pregnancy as a joint function of SRS (continuous) and nicotine dependence score (HSI, panels a, c; ND-sx, panels b, d), stratified by prospective (panels a, b) versus retrospective (panels c, d) prediction. The

interaction between HSI and SRS was statistically significant for prospective prediction (HSI-prospective: OR: 0.39, 95% CI [0.170, 0.876]; HSI-retrospective: OR: 0.54, 95% CI [0.256, 1.15]). The interaction between ND-sx count and SRS was trend-level significant (ND-sx prospective: OR:0.40, 95% CI [0.168, 0.961], ND-sx retrospective: OR:0.64, 95% CI [0.323, 1.28]). Four major conclusions may be drawn from the figure. First, confirmation of HSI-score as a superior predictor of smoking during pregnancy risk, shown by greater separation of the smoking during pregnancy predicted probability curves as a function of level of nicotine dependence at every level of sociodemographic risk. Second, the probability curves show greatly diminished separation at high levels of sociodemographic risk, indicating that at high levels of sociodemographic risk, degree of nicotine dependence at research interview is a much weaker predictor of outcome. Third, there is broad consistency of findings regardless of whether reporting of nicotine dependence occurred after or before first childbirth (i.e., retrospectively or prospectively). Lastly, the predictive utility of nicotine dependence shows a trend towards strengthened prospective versus retrospective prediction.

#### 4. Discussion

##### 4.1. Conclusions

Characterizing influential sociodemographic, individual, and environmental risk-factors for failure of smoking cessation during pregnancy is important for improving intervention efforts. We used nicotine dependence data from research cohort of female twins, combined with the birth records of children born to these twins, to investigate the predictive utility for smoking during pregnancy by proximal sociodemographic variables recorded on the birth record, nicotine dependence measured in a research setting, and their interaction. Consistent with previous research, we found that birth record data on education, marital status, age, and parity, were significant predictors of smoking during pregnancy. The best predictors of smoking during pregnancy were SRS, HSI, their two-way interaction, and a single item assessing lifetime report of failing two or more smoking cessation attempts. The DSM-IV symptom count, DSM-IV-Nicotine Dependence diagnosis, and individual DSM-IV-Nicotine Dependence items all failed to improve prediction of smoking during pregnancy when accounting for SRS and HSI items. Our ability to prospectively predict smoking during pregnancy risk from smoking characteristics was stronger than retrospective prediction.

##### 4.2. Assessment of nicotine dependence in pregnancy

While both the DSM-IV-Nicotine Dependence and HSI aim to measure physiological nicotine dependence, the HSI is a shorter measure, requiring minimal resources to administer, containing the majority of the information important for predicting smoking during pregnancy. Our work is consistent with a previous report showing that prediction of late-pregnancy smoking status was best achieved by using both HSI items and failed pre-pregnancy quit attempts were associated with higher risk of late-pregnancy continued smoking (Kurti et al., 2016). This conflicts with reports from the general population, where the *time-to-first-cigarette* item is more important for predicting smoking cessation (Baker et al., 2007). This present report highlights aspects of smoking behavior associated with smoking during pregnancy risk, setting the stage for improved assessment of risk and identifying at-risk individuals to target for increased cessation support. We identified three aspects of smoking behavior most important for assessing smoking during pregnancy risk—how soon one smokes their first cigarette after waking, number of cigarettes smoked per day, and history of cessation attempts/number of failed attempts. Using this information about an individual’s smoking behavior in the context of their sociodemographic status—age, years of education completed, marital status/reproductive

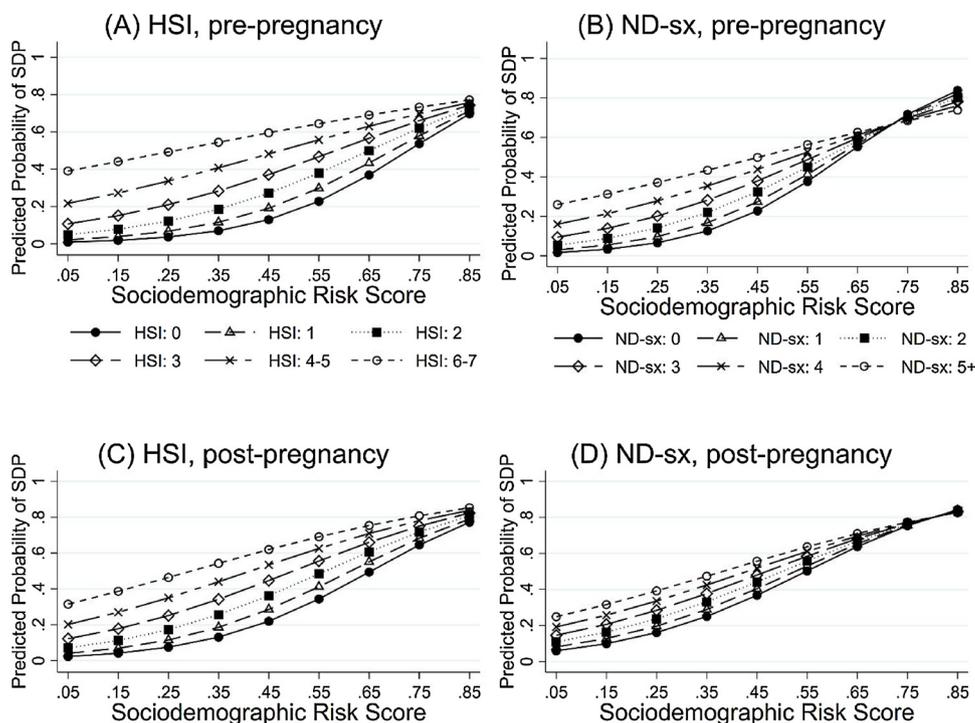


Fig. 1. Predicted probability of smoking during pregnancy as a function of sociodemographic risk score at time of pregnancy and of nicotine dependence measured either prior to or after first pregnancy.

Interaction between Nicotine Dependence measure (Heaviness of Smoking Index score or DSM-IV-Nicotine Dependence symptom count), assessed during late teens/early twenties from research data and sociodemographic risk score, estimated using birth record data at time of childbirth, in predicting SDP. Analyses are separated by whether assessment of Nicotine Dependence occurred before or after first pregnancy. In panels A) and C), the interaction between HSI score and sociodemographic risk score (continuous) is presented, separated by timing of first pregnancy relative to follow-up interview. In panels B) and D), the interaction between sextiled DSM ND-sx count and sociodemographic risk score (continuous) is presented, separated by timing of first pregnancy relative to follow-up interview. As sociodemographic risk increases, the importance of HSI as a predictor of future SDP is diminished. The strength of this relationship is weakened for ND-sx relative to HSI. Smoking assessment prior to first pregnancy: N = 589 births; smoking assessment after first pregnancy: N = 1048 births. (ND-sx: DSM-IV Nicotine Dependence Symptom Count; HSI: Heaviness of Smoking Index).

partner support, and history of prior pregnancy and childbirth, yields important information for providers in determining smoking during pregnancy risk and indicates need for smoking cessation intervention. Importantly, given our observed strengthened prospective prediction, our results support the importance of beginning screening years in advance of first pregnancy, thus maximizing opportunities to achieve successful smoking cessation prior to pregnancy.

The predictive utility of nicotine dependence measures was substantially diminished in individuals with intermediate-high sociodemographic risk, and this result was consistent in both prospective and retrospective analyses. Since more severe dependence is associated with greater difficulty quitting, including in pregnancy (Riaz et al., 2018), this implies an important health disparities challenge: the failure to accomplish cessation for sociodemographically disadvantaged pregnant individuals, despite lower levels of nicotine dependence, which should otherwise facilitate successful quitting. Our results suggest that nicotine dependence is not the sole indicator of smoking during pregnancy risk, and for some patients, sociodemographic risk proximal to time of childbirth may explain more risk for smoking during pregnancy. In their review, Boucher and Konkle (2016) emphasize the role of socioeconomic status, nicotine dependence, social support, culture, mental health, and access to health services as important contributors to smoking during pregnancy risk and emphasize pregnancy as an important point of contact for smoking cessation services to be delivered to patients. Less than half of patients report that their healthcare providers discourage their continued smoking during pregnancy (Hoekzema et al., 2014), despite evidence that two or more healthcare providers asking about smoking status increases odds of a past-year quit attempt and increased intention to quit in the next six months in the general population (An et al., 2008). Our results corroborate the need to address factors other than nicotine dependence as an important focus of patient-centered care and intervention efforts. In a recent analysis of the same data, we demonstrated unique risk of smoking during pregnancy associated with relationship/marital status at time of birth (Waldron et al., 2017).

### 4.3. Combining research and administrative data in health research

The analytic framework presented in this report is applicable to a broad array of health problems, where research data and administrative (e.g., birth record, driver's license) datasets can be combined to yield important insights not achieved in analyses considering only one data type. Our analyses of phenotype-environment interaction, predicting smoking during pregnancy as a joint function of nicotine dependence and environmental risk-factors at time of pregnancy, illustrate a framework that can be extended to other questions of interaction between individual and environmental risk: identify key environmental domains to test for interaction effects on cessation failure in addiction; on continued weight gain or failure of weight-loss efforts in obesity; or on relapse/recurrence risk across a broader range of psychiatric phenotypes. Such an approach can then be used to guide genotype-interaction analyses in genetic association data, or twin/family study data, supplementing preexisting research data with administrative data at modest cost.

### 4.4. Limitations

First, our analyses include only white non-Hispanic mothers due to limited numbers of African American twin pairs. It is important that future research identifies both risk and protective factors for groups experiencing higher rates of smoking during pregnancy and associated risk factors (e.g., Native Americans; CDC, 2018; Curtin and Matthews, 2016). Second, while aggregate birth record data are useful for understanding predictors of smoking during pregnancy, individual cases of both false positive and, more frequently, false negative reports can be identified. While some under-reporting of smoking during pregnancy is anticipated, this does not appear to be a major problem in our data. Some age x education combinations report rates as high as 60% (e.g., white non-Hispanic mothers, less than high school education, giving birth in their early 20s; data available on request), compared to the 8.4% national average. Moreover, underestimation of smoking during

pregnancy rates does not change observed effect estimates between smoking during pregnancy and offspring outcomes (Bakker et al., 2011). Third, while identifying individual factors associated with smoking during pregnancy risk is important for intervention efforts, this risk undoubtedly reflects an interplay of sociodemographic risks, history of exposure to neighborhoods with high rates of smoking during pregnancy, and other individual (including genetic, psychiatric history) and family-of-origin effects which may be only partially mediated through nicotine dependence. The present report does not address important aspects of social influence, either by reproductive partner, cohabitants during pregnancy, or neighborhood rates of smoking during pregnancy. We include reproductive partner influence obliquely, by analyzing the effect of marital status, but future research would benefit from more thorough analysis of these influences and their effect on achieving successful smoking cessation by time of pregnancy. Fourth, there is relatively high rates of co-use of tobacco and other drugs, especially cannabis and alcohol, during pregnancy (Dukes et al., 2017; Oga et al., 2018). Future research should examine the roles of substance use and dependence, including, alcohol, marijuana, illicit substances, and electronic nicotine delivery systems, on risk for cigarette use during pregnancy. This would further inform how healthcare providers should use assessment of alcohol and other substance use during pregnancy to tailor risk assessment and treatment. Finally, lower levels of nicotine dependence may become more severe over time. Future work could address this by examining changes in sociodemographic risk and nicotine dependence between pregnancies and evaluate the roles of sociodemographic risk and nicotine dependence in sister-sister discordance for smoking during pregnancy.

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### Contributors

Heath, Madden, and Bucholz designed the study and wrote the protocol. Houston-Ludlam conducted the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

### Conflict of interest

No conflict declared.

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### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2019.02.014>.

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