Preventive Medicine 128 (2019) 105709

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

A review of tobacco regulatory science research on vulnerable populations

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ARTICLE INFO

Keywords:
Cigarettes
Tobacco
Nicotine
Tobacco regulatory science
Vulnerable populations
Adults

ABSTRACT

In 2013 the U.S. Food and Drug Administration and National Institutes of Health established fourteen Tobacco Centers of Regulatory Science (TCORS) to advance scientific knowledge relevant to conducting evidence-based tobacco regulation. This report reviews TCORS-funded research with adult vulnerable populations. The literature search included a list of all TCORS-funded publications compiled by the TCORS coordinating center; all TCORS were requested to share publications not in the coordinating-center's list. Only TCORS-funded reports describing an empirical study with an adult vulnerable population published in a peer-reviewed journal between September 2013 and June 2018 were included. 71 reports met inclusion criteria; 39% (28/71) examined tobacco use among those with mental health and medical comorbidities, 34% (24/71) socioeconomic disadvantage, 31% (22/71) women of reproductive age, 30% (21/71) racial/ethnic minorities, 18% (13/71) rural residents, and 3% (2/71) each among active military/veterans and sexual/gender minorities. Regarding scientific domains, 63% (45/71) investigated behavior, 37% (26/71) addiction, 24% (17/71) health effects, 20% (14/71) impact analyses, 18% (13/71) toxicity, 8% (6/71) marketing influences, and 7% (5/71) communications. Totals exceed 100% because some reports addressed multiple populations/domains. TCORS funding has generated a substantial, multidisciplinary body of new scientific knowledge on tobacco use in adult vulnerable populations. However, considerable variability was noted in the amount of research conducted across the various vulnerable populations and scientific domains. Most notably, relatively few studies focused on active military/veterans or sexual/gender minorities, and the scientific domains of marketing influences and communications were conspicuously underrepresented. These are important knowledge gaps to address going forward.

1. Introduction

In 2013, fourteen Tobacco Centers of Regulatory Science (TCORS) were established at universities and medical institutions throughout the US (FDA, 2013). This seminal, federally-supported initiative promoted research that informs the regulation of tobacco products nationwide. The TCORS have been referred to as the centerpiece of the Tobacco Regulatory Science Program (TRSP), a collaboration between the National Institutes of Health (NIH) and Food and Drug Administration (FDA) Center for Tobacco Products (CTP) (Office of Disease Prevention, 2018). More specifically, the mission of the TCORS and TRSP is to support a program of sound multidisciplinary research relevant to the 2009 Tobacco Control Act, which gave FDA regulatory authority over the manufacture, distribution, and marketing of tobacco products with the overarching aim of protecting the U.S. public from the adverse health impacts of tobacco use (United States, 2009). With recent completion of the initial five years of TCORS support, there is value in reviewing the research activities and associated regulatory and scientific implications that have been supported by this considerable effort. As a step in that direction, this report reviews TCORS-funded research on tobacco use among adult populations that are especially vulnerable to tobacco use, addiction, and adverse health impacts, a crosscutting

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https://doi.org/10.1016/j.ypmed.2019.04.024
Received 30 January 2019; Received in revised form 22 April 2019; Accepted 28 April 2019
Available online 02 May 2019

Table 1
Definitions and research priorities for CTP scientific domains.[1]

	Definition	Priorities
Toxicity	Understanding how tobacco products and changes to tobacco product characteristics affect their potential to cause morbidity and mortality, including animal and cell culture models, as well as novel alternative toxicology approaches that test the toxicity of tobacco smoke, aerosols, or specific constituents in tobacco.	• Toxicological assays (in vivo and in vitro) to compare toxicity across different types of tobacco products within the same class, including electronic nicotine delivery systems (ENDS), cigars, waterpipes, and smokeless tobacco; • How product design characteristics (and changes in those characteristics) impact constituent exposure and toxicity from tobacco products; • Biomarkers to assess exposure, as well as biomarkers to assess harm or toxicity of non-cigarette tobacco products, including ENDS.
Addiction	Understanding the effect of tobacco product characteristics on addiction and abuse liability.	• Impact of changes in tobacco product characteristics (such as flavors or product design) on dependence; • Differences in dependence and tobacco use patterns with use of low-nicotine-content cigarettes in context with other tobacco products; • The amounts of nicotine delivered to ENDS users during experimentation, regular ENDS use, dual use of ENDS and cigarettes, and cigarette smoking quit attempts; • Correlation of ENDS use behaviors with pharmacokinetic and pharmacodynamics effects of nicotine and other HPHCs delivered by ENDS.
Health effects	Understanding the short- and long-term health effects of tobacco products. Highest priority areas include cardiovascular or respiratory health effects, including inflammation. Other health effects including cancer, oral health, or reproductive health may be included within projects, but should not be the primary focus of the TCORS.	• Impact of changes in tobacco product characteristics (such as flavors or product design) on human health; • Biomarkers to assess short- and long-term effects of non-cigarette tobacco products; • Clinical evaluations to distinguish changes in cell function/physiology specific to tobacco exposure (e.g., ENDS aerosol exposure) known to indicate longer-term disease development and progression.
Behavior	Understanding the knowledge, attitudes, and behaviors related to tobacco product use and changes in tobacco product characteristics.	• Changes in tobacco product characteristics (such as flavors, product design, or packaging) impact on tobacco use behaviors, including experimentation, initiation, dual/poly use, transition to non-flavored products, and cessation; • Innovative methods and measures to assess tobacco use behaviors; • Measures, methods, or study designs to assess the likely impact of novel and/or potential modified risk tobacco products on tobacco behavior, including perceptions, susceptibility, experimentation, adoption, switching, and use (including dual use); • Measures (e.g., attitudes, perceptions, intentions) to best predict future behaviors of non-cigarette tobacco product use, including current and established users of cigars, waterpipe, and ENDS.
Communications	Understanding how to effectively communicate to the public and vulnerable populations regarding nicotine and the health effects of tobacco products, including media campaigns and digital media.	• Messages to effectively communicate about nicotine and the harms of non-cigarette tobacco product use; • Methods and messages for communicating complex scientific concepts to the general public, including risk and harms of tobacco use, taking into account unintended consequences; • Effectiveness of text and graphic warnings for tobacco products other than cigarettes.
Marketing influences	Understanding why people become susceptible to using tobacco products (both classes of products and products within classes) and to transitions between experimentation and initiation to regular use and dual use. Topics may include tobacco industry marketing such as advertising, point-of-sale, digital media, and promotions.	• Methods, measures, and study designs to best assess the impact of tobacco product advertising and promotion restrictions on users and non-users of tobacco, including marketing of novel and/or potential modified risk tobacco products; • Impact of potential marketing restrictions on youth experimentation, initiation, use, and cessation.
Impact analysis	Understanding the impact of potential FDA regulatory actions.	• Evaluation of policies at the state and community level that fall within FDA CTP regulatory authorities; • Methods and measures (e.g., behavioral economics, population modeling) to estimate the range of potential impacts on behavior and health of potential FDA regulatory actions such as products standards addressing toxicity, appeal, and addiction.

[1] Domain details are from RFA-OD-17-003 (Department of Health and Human Services, 2017).

theme of the TCORS.

Tremendous progress has been made in reducing the prevalence of tobacco use and its adverse health impacts since the landmark publication of the 1964 U.S. Surgeon General's report on smoking and health (Office of the Surgeon General (US), 1964), including substantial reductions in smoking prevalence, per capita cigarette consumption, and smoking-attributable death and disease (Schroeder and Koh, 2014; U.S. Department of Health and Human Services, 2014). Unfortunately, these decreasing trends have leveled off in the past decade (U.S. Department of Health and Human Services, 2014). Moreover, the overall decreases were unevenly distributed across the U.S. population, with considerable decreases evident among the more affluent and educated, but less so or not at all among those who are socioeconomically disadvantaged, have psychiatric conditions, reside in rural regions, or are from racial/ethnic or gender/sexual minority groups (Cepeda-Benito et al., 2018; Doogan et al., 2017; Higgins, 2014; Higgins et al., 2016; Hiscock et al., 2012; Roberts et al., 2017; Schroeder, 2016). Additionally, these vulnerabilities intersect in clusters or profiles that can confer especially high risk (Higgins et al., 2016; Gaalema et al., 2018b). For example, socioeconomically disadvantaged women of reproductive age represent a subgroup of particular concern because they are at increased risk for initiating smoking, failing to quit smoking during pregnancy, and associated serious adverse effects on pregnancy outcomes and infant health (Higgins and Chilcoat, 2009; Kandel et al., 2009). Importantly, this unevenness in prevalence of cigarette smoking and other tobacco product use is a major contributor to the growing problem of health disparities (Schroeder, 2016; Higgins, 2014; Higgins, 2015). Additionally, the number and variety of available

tobacco and nicotine-delivering products has increased rapidly over the last decade, introducing novel use patterns, and raising important research questions and regulatory challenges regarding, for example, the net-population level impact of new products and developing and enforcing policies in a dynamic marketplace (Gottlieb and Zeller, 2017). This narrative review focuses on TCORS-supported empirical studies explicitly focused on tobacco use in adult vulnerable populations published in peer-reviewed journals between September 2013 when TCORS funding was initiated through June 2018 when our literature search was completed. Reports on youth/young adults are being covered in a parallel review (Perry et al., in press) and hence were excluded from the report. Vulnerable populations were defined in this review as individuals with mental health/medical comorbidities, socioeconomic disadvantage, pregnant women and women of reproductive age, racial and ethnic minorities, rural populations, active military and veterans, and sexual and gender minorities in accordance with the definition noted in TCORS RFAs (Department of Health and Human Services, 2013; Department of Health and Human Services, 2017). While not meant to represent an exhaustive list, these populations share an increased risk for tobacco use and addiction or for experiencing adverse health effects from tobacco use.

2. Methods

2.1. Search strategy

The search for reports relevant to this review included two components: First, the TCORS coordinating center (Center for Evaluation and Coordination of Training and Research, CECTR) shared a list of citations for all TCORS-funded publications through December 2017, copies of which were downloaded from PubMed. Second, all TCORS Principal Investigators were contacted in June 2018 with a request to share any TCORS-supported publications involving vulnerable populations that were not included in the CECTR list.

Next, publications identified for potential inclusion were reviewed by at least two authors. For inclusion, articles had to report a previously unpublished empirical study, be published in a peer-reviewed journal, be funded by one of the TCORS, and explicitly focus on a vulnerable population. The criterion of explicitly focusing on a vulnerable population was operationally defined as mentioning the population in the report Title, Abstract, or text of the Results section; mention of the population only in a table or figure was insufficient for inclusion. Disagreements were resolved through discussion until a consensus was reached.

2.2. Categorizing reports by populations and scientific domains examined

All reports were reviewed by at least two authors to identify which vulnerable population(s) and FDA scientific domain(s) were examined. The seven vulnerable populations of interest are listed above; the seven scientific domains were the following topics prioritized in the TCORS RFAs: addiction, behavior, communications, health effects, impact analysis, marketing influences, and toxicity (Department of Health and Human Services, 2013; Department of Health and Human Services, 2017). Domains are defined in Table 1. Disagreements were resolved through discussion until a consensus was reached.

3. Results

3.1. Overall search

The search identified 788 reports. Forty-three reports were excluded as duplicates, 490 because they did not involve a vulnerable population or were outside the FDA CTP scope, 166 because they focused on youth/young adults, and 18 for not reporting results of an empirical study (e.g., commentaries, literature reviews) leaving 71 reports that met all inclusion criteria (Supplemental Table) (Cepeda-Benito et al., 2018; Doogan et al., 2017; Higgins et al., 2016; Roberts et al., 2017; Nemeth et al., 2018; White et al., 2016; Stanton et al., 2016; Hefner et al., 2016; Spears et al., 2016; Miller et al., 2017; Higgins et al., 2017a; Parker et al., 2018; Gaalema et al., 2018a; Stokes et al., 2018; Tidey et al., 2013; Tidey et al., 2016; AhnAllen et al., 2015; Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c; Higgins et al., 2018; Tidey et al., 2017; Valentine et al., 2018; Jamal et al., 2014; Veal et al., 2017; Gaalema et al., 2017; Legro et al., 2014; Cooper et al., 2018; White et al., 2018; Nayak et al., 2016; Shang et al., 2017; Lopez et al., 2018; Roberts et al., 2016a; Chivers et al., 2016; Brasky et al., 2018; Bergeria et al., 2018; White et al., 2014; Vurbic et al., 2015; Klein et al., 2015; Lee et al., 2015; Roberts et al., 2015; Kurti et al., 2018a; Kurti et al., 2018b; Kurti et al., 2017; Higgins et al., 2017d; Heil et al., 2014; White et al., 2015; Higgins et al., 2017e; Taghavi et al., 2018a; Taghavi et al., 2018b; Phillips et al., 2018; Vurbic et al., 2014; Sims et al., 2016; Leigh et al., 2017; Hall et al., 2016; Garcia et al., 2016; Kamimura et al., 2018; Murphy et al., 2017; Choi et al., 2017; Baezconde-Garbanati et al., 2017; Roberts et al., 2016b; Curry et al., 2017; Doogan et al., 2018; Davison et al., 2016; Klein et al., 2017; Roberts et al., 2016c; Nayak et al., 2017; Cohn et al., 2018; García et al., 2016; Tidey et al., 2014; Streck et al., 2018). These 71 reports include 28 (39%) addressing Mental Health and Medical Comorbidities (Table 2), 24 (34%) addressing Socioeconomic Status (Table 3), 22 (31%) on Pregnant Women and Women of Reproductive Age (Table 4), 21 (30%) on Race/Ethnicity (Table 5), 13 (18%) on Rural Residents (Table 6), and 2 (3%) each on Active Military/Veterans and Sexual/Gender Minorities (detailed in text below). Those totals exceed 71 (100%) because some reports address more than one population. Regarding scientific domains, 45 (63%) investigate behavior, 26 (37%) addiction, 17 (24%) health effects, 14 (20%) impact analysis, 13 (18%) toxicity, 6 (8%) marketing influences, and 5 (7%) communications (Supplemental Table). Again, these values exceed 71 (100%) because some reports investigate multiple domains. Summaries of reports pertaining to each vulnerable population are reviewed below.

3.2. Mental health and medical comorbidities

In the U.S., people with mental health conditions (MHCs) and medical comorbidities are at heightened risk for tobacco-related mortality compared to people without these comorbidities (U.S. Department of Health and Human Services, 2014; Callaghan et al., 2014). The 28 (39%) reports investigating this vulnerable population addressed topics relevant to the addiction, health effects, behavior, impact analysis, and toxicity domains (Supplemental Table, Table 2). No reports addressed communications or marketing influences.

Included among the 24 reports addressing the behavior domain (Higgins et al., 2016; Nemeth et al., 2018; White et al., 2016; Stanton et al., 2016; Hefner et al., 2016; Spears et al., 2016; Miller et al., 2017; Higgins et al., 2017a; Parker et al., 2018; Gaalema et al., 2018a; Stokes et al., 2018; Tidey et al., 2013; Tidey et al., 2016; AhnAllen et al., 2015; Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c; Higgins et al., 2018; Tidey et al., 2017; Valentine et al., 2018; Gaalema et al., 2017; Legro et al., 2014; Tidey et al., 2014; Streck et al., 2018) were studies examining MHCs or medical comorbidities as predictors of tobacco use. Converging evidence across five studies involving U.S. national surveys (National Survey on Drug Use and Health, NSDUH; Population Assessment of Tobacco and Health, PATH; Tobacco Products and Risk Perceptions Survey, TPRPS) (Higgins et al., 2016; White et al., 2016; Stanton et al., 2016; Spears et al., 2016; Higgins et al., 2017a) and two surveys focused on a random sample of rural residents (Nemeth et al., 2018) and clinical sample of veterans (Hefner et al., 2016), demonstrate that the presence or severity of a MHC is independently associated with increased odds of cigarette or other tobacco use. Two other studies using national surveys (NSDUH) demonstrate that MHCs predict greater odds of using higher over lower-nicotine yield cigarettes

Table 2
Characteristics of studies focused on Mental Health Conditions/Medical Comorbidities.

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Higgins et al. (2016)	U.S. National Sample	2011–2013	114,426 (19%)	Three years of cross-sectional NSDUH[3] survey data were pooled to examine risk factors for current smoking. Age, gender, race/ethnicity, educational attainment, poverty, alcohol use disorders, substance use disorders and mental illness were all independently associated with smoking; effects of risk-factor combinations were typically summative.	Cigarettes	Behavior
Nemeth et al. (2018)	Rural women in Ohio	2012–2013	401 (100%)	Cross-sectional data were used to examine risk factors for cigarette use. Younger age, greater depressive symptom severity, greater normative acceptance of smoking and greater neighborhood cohesion increased risks for current smoking.	Cigarettes	Addiction, Behavior
White et al. (2016)	U.S. National Sample	2012	37,869 (51.9%)	Cross-sectional NSDUH survey data were used to examine risk factors for current cigarette and SLT[4] use. Past year diagnosis of major depressive disorder, along with other demographic predictors, contributed to odds of smoking but not SLT use. Dependence on alcohol, marijuana, heroin, and cocaine were associated with cigarette use; all except cocaine dependence were also associated with SLT use.	Cigarettes, SLT	Behavior
Stanton et al. (2016)	U.S. National Sample	2005–2013	335,080 (51.9%)	Nine years of cross-sectional NSDUH survey data were pooled to examine whether chronic medical and mental health conditions were associated with current use of cigarettes, cigars, pipes, or SLT. Cigarette use was higher and stable over time among those with comorbidities, mental health and substance use disorders, whereas use declined among those without comorbidities. Cigar and pipe use were higher among those with comorbidities and were stable over time; SLT increased over time in all.	Cigarettes Cigars, SLT, Pipes	Behavior
Hefner et al. (2016)	VA patients in Connecticut	2015	188 (10%)	A convenience sample of smokers was used to compare characteristics of ENDS[5] users and non-users and perceptions of ENDS. ENDS users (30.9% of sample) were more likely to have a mental health disorder and less likely to have an alcohol use disorder than non-users.	ENDS	Addiction, Behavior
Spears et al. (2016)	U.S. National Sample	2015	6051 (51.4%)	Cross-sectional survey of ENDS use in people with and without lifetime mental health conditions (MHCs). People with MHCs, particularly former smokers, were more likely to use ENDS, and former smokers with MHCs are more likely to report having used ENDS during smoking quit attempts than those without a MHC.	Cigarettes, ENDS	Behavior
Miller et al. (2017)	U.S. National Sample	2013–2014	32,320 (51.9%)	Data from Wave 1 of the PATH[6] survey were used to examine relationships between self-perceived mental health and tobacco use. Poorer self-perceived mental health was associated with increased cigarette, ENDS, cigarillo, filtered cigar and SLT use, but not increased traditional cigar use; motives for use were similar across mental health status conditions.	Cigarettes, ENDS, Cigars, Cigarillos, SLT	Behavior
Higgins et al. (2017a)	U.S. National Sample	2011–2013	114,426 (NR)[7]	Three years of cross-sectional NSDUH survey data were pooled to examine risk factors for smoking higher- vs. lower-nicotine yield cigarettes. Age, gender, race/ethnicity, educational attainment, poverty, substance use disorders and mental illness were independent risk factors for using higher-nicotine cigarettes, and use of higher-nicotine cigarettes increased risk for nicotine dependence.	Cigarettes	Addiction, Behavior
Parker et al. (2018)	U.S. National Sample	2006–2014	58,971 (43.4%)	Nine years of cross-sectional NSDUH survey data were pooled to examine nicotine dependence severity as a function of OD[8] status. Smokers with OD had greater severity of nicotine dependence and were more likely to be nicotine dependent than those without OD. The relationship between OD and nicotine dependence was attenuated but remained significant after adjusting for variables that differed between groups, such as depression, anxiety, alcohol, and other substance use.	Cigarettes	Addiction, Behavior
Gaalema et al. (2018a)	U.S. National Sample	2013–2015	23,262 (47%)	Data from Waves 1 and 2 of the PATH study were used to compare tobacco use and attitudes as a function of level of cardiac risk. Use of		Behavior

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Table 2 (*continued*)

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
				combusted tobacco was higher among those with lifetime myocardial infarction (MI). Having a recent MI was associated with increased perception of tobacco harms and with increased quit or reduction attempts, but not with successful quitting or reduction.	Cigarettes, ENDS, Cigars, SLT, Snus, Pipe, Dissolvables, Hookah	
Stokes et al. (2018)	U.S. National Sample	2014	4933 (54.2%)	Cross-sectional NHIS[9] data were used to examine prevalence and patterns of ENDS use among adults with a history of cardiovascular disease (CVD). ENDS use was associated with past-year quitting and past-year quit attempts.	Cigarettes, ENDS	Behavior
Tidey et al. (2013)	Smokers with schizo-phrenia and controls in Rhode Island	NR	56 (41%)	Double-blind, mixed-factors laboratory assessment of responses to VLNC[10] cigarettes with placebo or 42?mg nicotine replacement (NRT). VLNC cigarettes combined with either placebo or NRT reduced craving, withdrawal symptoms, and usual brand smoking in both populations; VLNC cigarettes were less satisfying and rewarding than usual brand.	Research cigarettes	Addiction, Behavior
Tidey et al. (2016)	Smokers with schizo-phrenia and controls in Rhode Island	NR	50 (46.5%)	Double-blind, mixed-factors laboratory assessment of responses to VLNC cigarettes with placebo or 42?mg nicotine replacement (NRT). Use of VLNC cigarettes increased puff duration and reduced time between puffs, but participants smoked fewer puffs, resulting in net decreases in volume of total smoke intake.	Research cigarettes	Addiction, Behavior, Toxicity
AhnAllen et al. (2015)	Smokers with schizo-phrenia and controls in Rhode Island	NR	57 (40%)	Double-blind, mixed-factors laboratory assessment of responses to VLNC cigarettes with placebo or 42?mg nicotine replacement (NRT). Compared to a usual brand smoking condition, use of VLNC?+?placebo patches impaired cognitive performance in several domains; these impairments were reversed in the VLNC?+?NRT condition.	Research cigarettes	Behavior
Higgins et al. (2017a)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Multi-site, double-blind, within-participant laboratory assessment of subjective and behavioral responses to cigarettes varying in nicotine content. Reducing the nicotine content of cigarettes reduced subjective and behavioral indicators of cigarette addiction liability across populations.	Research cigarettes	Addiction, Behavior, Impact Analysis, Toxicity
Arger et al. (2017)	Smokers with affective disorders, opioid depend-ence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Secondary analysis of a multi-site, double-blind, within-participant laboratory assessment of responses to cigarettes varying in nicotine content. Across populations, Satisfaction and Aversion subscale scores on the Modified Cigarette Evaluation Questionnaire predicted cigarette choices as measured using a concurrent-choice behavioral task.	Research cigarettes	Addiction, Behavior, Impact Analysis
Higgins et al. (2017a)	Smokers with affective disorders, opioid depend-ence, and low SES women in Vermont, Rhode Island, and Maryland	2014–2015	26 (77%)	Multi-site, double-blind, within-participant laboratory assessment of subjective and behavioral responses to cigarettes varying in nicotine content. Across populations, participants rated the VLNC cigarettes lower in satisfaction and made fewer choices for these puffs relative to NNC cigarette puffs in concurrent choice testing. All cigarettes reduced withdrawal symptoms and none increased puff intensity.	Research cigarettes	Addiction, Behavior, Impact Analysis
Higgins et al. (2018)	Smokers with affective disorders, opioid depend-ence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Secondary analysis of a multi-site, double-blind, within-participant laboratory assessment of responses to cigarettes varying in nicotine content, in which dependence severity was examined as a moderator of responses. Across populations, dependence severity did not moderate effects of nicotine content on measures of addiction liability or withdrawal, and had minimal effects on craving and topography.	Research cigarettes	Addiction, Behavior, Impact Analysis, Toxicity

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Table 2 (*continued*)

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Tidey et al. (2017)	Daily smokers from 10 sites	2013–2014	717 (42.3%)	Secondary analysis of a multi-site, double-blind, randomized trial, in which depressive symptom severity was examined as a moderator of responses to normal-nicotine content (NNC) vs. VLNC cigarettes over a 6-week period. Effects of VLNC cigarettes on smoking were not moderated by depressive symptom severity. Among smokers with higher depression at baseline, those assigned to VLNC cigarettes had lower depression at week 6 than those assigned to NNC cigarettes.	Research cigarettes	Addiction, Behavior, Impact Analysis, Toxicity
Valentine et al. (2018)	Veteran smokers with psych-iatric or substance use disorders	NR	43 (7%)	Open label study of ENDS provision (tank style; 12 or 24?mg/ml nicotine) on cigarette use over a 4-week period. Mean frequency of ENDS use was 5.7?days/week; significant reductions in cigarette use, dependence, and carbon monoxide levels, and increases in motivation to quit, were observed over time.	ENDS	Addiction, Behavior, Impact Analysis, Toxicity
Jamal et al. (2014)	Brazilians undergoing mandatory occupational health evaluation	NR	5503 (21.2%)	Cross-sectional study examining relationships between smoking and metabolic syndrome (MetS) on risk factors for cardiovascular disease (CVD). The prevalence of MetS was higher among smokers than non-smokers, and smoking increased the risk of systemic inflammation among those with MetS.	Cigarettes	Health Effects
Veal et al. (2017)	Women with ductal carcinoma in situ (DCIS) in Wisconsin	1997–2006	1925 (100%)	Longitudinal cohort study examining associations between body mass index, physical activity, alcohol consumption and smoking with mortality. All-cause and cancer-specific mortality were elevated among women who smoked pre-and post-diagnosis; all-cause mortality was reduced among women with greater levels of physical activity.	Cigarettes	Health Effects
Legro et al. (2014)	Women with polycystic ovary syndrome (PCOS) seeking fertility treatment	NR	626 (100%)	Secondary analysis of a large randomized controlled study of infertility treatments in women with PCOS that examined whether smoking status was related to risk of infertility and response to infertility treatment. A subsample was used to validate self-reported smoking status with cotinine level. Current smoking was associated with a more severe phenotype at baseline and a lower treatment response in terms of metabolic and reproductive risk factors.	Cigarettes	Behavior, Health Effects
Cooper et al. (2018)	Pregnant women in Vermont	NR	93 (100%)	Analyzed effects of a randomized controlled trial of effects of abstinence-contingent vouchers on relationships between smoking, uterine blood flow and birth outcomes. No direct relationship between smoking and uterine artery hemodynamics was demonstrated. Volumetric flow was an independent contributor to birth weight and associated with fetal fat deposition; smoking was not independently associated with either outcome.	Cigarettes	Health Effects
White et al. (2018)	African Americans in Mississippi	2000–2013	2991 (56.1%)	Longitudinal analysis of Jackson Heart Study examining associations between smoking and developing diabetes mellitus among those without diabetes mellitus at baseline. Baseline heavy smoking (20 or more cigarettes per day) and smoking pack-years were associated with increased risk of developing diabetes. Adjusting for waist circumference and hs-CRP minimally attenuated the incidence rate.	Cigarettes	Health Effects
Tidey et al. (2014)	Smokers with schizo-phrenia and controls in Rhode Island	NR	55 (40%)	Double-blind, mixed-factors laboratory comparison of effects of 3-day smoking abstinence and reinstatement in smokers with and without schizophrenia. Smokers with schizophrenia had higher craving and withdrawal symptoms during abstinence, greater nicotine preference after abstinence, and relapsed sooner than controls.	Cigarettes	Behavior

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Table 2 (*continued*)

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Streck et al. (2018)	Smokers with opioid dependence and controls in Vermont	NR	72 (42%)	Comparison of tobacco withdrawal symptoms among smokers with OD and those without substance use disorders who had received monetary incentives to experimentally induce smoking abstinence. Smokers with OD reported higher craving and withdrawal than controls prior to abstinence but both groups had similar reductions in withdrawal symptoms over time. Female controls had the greatest increase in craving after abstinence.	Cigarettes	Behavior

[1] Shared superscripts indicate shared samples across studies.
[2] All of the studies described the gender/sex breakdown of their participants as male and/or female or as men and/or women. The studies did not address whether participants self-reported their assigned sex at birth and/or their gender identity at the time of the survey.
[3] National Survey on Drug Use and Health.
[4] Smokeless tobacco.
[5] Electronic Nicotine Delivery System.
[6] Population Assessment of Tobacco and Health.
[7] Data not reported or could not be determined.
[8] Opioid dependence.
[9] National Health Interview Survey.
[10] Very low nicotine content.

(Higgins et al., 2017a) and greater tobacco dependence (Higgins et al., 2017a; Parker et al., 2018). Several reports also using NSDUH data demonstrated that chronic medical conditions including asthma (Stanton et al., 2016) and cardiovascular disease (Gaalema et al., 2018a) independently predict greater likelihood of tobacco product use. In sum, these reports provide compelling evidence that these comorbidities are associated with increased risk for tobacco use and dependence, and suggest that current tobacco control policies may be less effective among smokers with MHCs and medical comorbidities.

Two studies (Spears et al., 2016; Stokes et al., 2018) using data from national surveys (National Health Interview Survey, NHIS and TPRPS) reported that electronic cigarette use is associated with past-year quitting or quit attempts among people with MHCs or medical comorbidities, although the cross-sectional nature of these surveys precludes causal inferences about the role of e-cigarettes in quitting. In addition, an open-label study (Valentine et al., 2018) of e-cigarette provision over a 4-week period in a clinical sample of veterans with MHCs found that they were highly acceptable and reduced smoking, suggesting that controlled studies of e-cigarette effects on cigarette use in smokers with MHCs are warranted. However, results from one of the studies (Spears et al., 2016) in a nationally-representative sample also suggested that ENDS may attract former smokers with MHCs back to nicotine product use. Considered together, these studies suggest that comorbid smokers may find e-cigarettes an acceptable method for reducing tobacco use, but e-cigarette use among former smokers is a concern as it may lead to smoking relapse.

Eight studies that fell within the domains of behavior and addiction (Tidey et al., 2013; Tidey et al., 2016; AhnAllen et al., 2015; Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c; Higgins et al., 2018; Tidey et al., 2017) investigated the timely and important topic of reducing the nicotine content of cigarettes on smoking (Gottlieb and Zeller, 2017; Donny et al., 2015). A laboratory study comparing responses to very low nicotine content cigarettes (VLNCs) and usual-brand cigarettes in smokers with schizophrenia and controls demonstrated that while participants reported VLNCs less satisfying than usual-brand cigarettes, VLNCs nevertheless decreased craving, withdrawal, and smoke intake from usual-brand cigarettes (Tidey et al., 2013) without engendering compensatory smoking (Tidey et al., 2016). A secondary analysis demonstrated that transitions to VLNCs can negatively impact cognitive performance, but those decrements are reversed by transdermal nicotine (AhnAllen et al., 2015). Another series of studies experimentally examined acute effects of VLNCs in men and women with affective disorders, men and women with opioid dependence, and women with socioeconomic disadvantage (Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c). Across these populations, VLNCs decreased the positive reinforcing and subjective effects of smoking without engendering compensatory smoking (Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c). Moreover, these results were not moderated by cigarette mentholation or tobacco dependence severity (Higgins et al., 2017b; Higgins et al., 2018). Finally, a secondary analysis that examined effects of 6 weeks of exposure to VLNCs in smokers with higher vs. lower depressive symptoms demonstrated that VLNCs decreased smoking rate, dependence severity, and depressive symptoms (Tidey et al., 2017). Collectively, these studies indicate that an FDA-mandated reduction in the nicotine content of cigarettes to a minimally addictive level has the potential to reduce cigarette use among smokers with MHCs, with minimal or no unintended negative consequences. Future studies should examine whether access to non-combusted nicotine products may enhance the effects of a reduced-nicotine standard on smoking rates in smokers with MHCs. As effects of a reduced-nicotine standard have not been examined in smokers with medical comorbidities, this is also an important area for future research.

The five studies (Jamal et al., 2014; Veal et al., 2017; Gaalema et al., 2017; Legro et al., 2014; Cooper et al., 2018) falling within the health effects domain focused on understanding short- and long-term health

Table 3
Characteristics of studies focused on Low Socioeconomic Status (SES).

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Higgins et al. (2016)	U.S. National Sample	2011–2013	114,426 (19%)	Three years of cross-sectional NSDUH[3] survey data were pooled to examine risk factors for current smoking. Age, gender, race/ethnicity, educational attainment, poverty, alcohol use disorders, substance use disorders and mental illness were all independently associated with smoking; effects of risk-factor combinations were typically summative.	Cigarettes	Behavior
Roberts et al. (2017)	U.S. National Sample	2013–2014	32,320 (52%)	Compared prevalence of using traditional and emerging tobacco products using Wave 1 of the PATH[4] Study. Dual use of traditional tobacco products was more prevalent in rural than urban areas. Although emerging tobacco products were more prevalent among urban than rural subpopulations (e.g., e-cigarettes among men, hookah among women), rural/urban status did not reliably predict single or dual use of emerging tobacco products when adjusting for sociodemographic covariates.	Cigarettes, ENDS[5], Cigars, Cigarillos, SLT[6], Pipes, Hookah	Behavior
White et al. (2016)	U.S. National Sample	2012	37,869 (51.9%)	Cross-sectional NSDUH survey data were used to examine risk factors for current cigarette and SLT use. Past year diagnosis of major depressive disorder, along with other demographic predictors, contributed to odds of smoking but not SLT use. Dependence on alcohol, marijuana, heroin, and cocaine were associated with cigarette use; all except cocaine dependence were also associated with SLT use.	Cigarettes, SLT	Behavior
Stanton et al. (2016)	U.S. National Sample	2005–2013	335,080 (51.9%)	Trends in tobacco use among those with chronic health conditions were examined using NSDUH years 2005–2013. Cigarette smoking declined for adults without a chronic condition but stayed stable for those with one more conditions. Other tobacco product use either remained stable or increased overtime for adults with chronic conditions.	Cigarettes, Cigars, SLT, Pipe	Behavior
Higgins et al. (2017a)	U.S. National Sample	2011–2013	114,426 (NR)[7]	Three years of cross-sectional NSDUH survey data were pooled to examine risk factors for smoking higher- vs. lower-nicotine yield cigarettes. Age, gender, race/ethnicity, educational attainment, poverty, substance use disorders and mental illness were independent risk factors for using higher-nicotine cigarettes, with lower education being the strongest risk factor. Use of higher-nicotine cigarettes increased risk of dependence.	Cigarettes	Addiction, Behavior
Gaalema et al. (2018a)	U.S. National Sample	2013–2015	23,262 (47%)	PATH data (Waves 1 and 2) were used to assess tobacco use among cardiac patients and those with risk factors for heart disease. Smokers who had a recent or lifetime myocardial infarction (MI) believed that smoking was causing/worsening a health problem. Having a recent MI increased attempts to quit/reduce combustible cigarettes, but follow up data did not predict cessation of combusted product use at W2.	Cigarettes, ENDS, Cigars, SLT, Snus, Pipes, Dissolvables, Hookah	Addiction, Behavior
Higgins et al. (2017a)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Multi-site, double-blind, within-participant laboratory assessment of subjective and behavioral responses to cigarettes varying in nicotine content. Reducing the nicotine content of cigarettes reduced subjective and behavioral indicators of cigarette addiction liability across populations.	Research cigarettes	Addiction, Behavior, Impact Analysis, Toxicity
Arger et al., (2017)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Secondary analysis of a multi-site, double-blind, within-participant laboratory assessment of responses to cigarettes varying in nicotine content. Across populations, Satisfaction and Aversion subscale scores on the Modified Cigarette Evaluation Questionnaire predicted cigarette choices as measured using a concurrent-choice behavioral task.	Research cigarettes	Addiction, Behavior, Impact Analysis
Higgins et al. (2017a)	Non-pregnant smokers in Vermont	NR	9 (100%)	Multi-site, double-blind, within-participant laboratory assessment of subjective and behavioral responses to cigarettes varying in nicotine content. Across populations, participants rated the VLNC[8] cigarettes lower in satisfaction and made fewer choices for these puffs relative to NNC cigarette puffs in concurrent choice testing. All cigarettes reduced withdrawal symptoms and none increased puff intensity.	Research cigarettes	Addiction, Behavior, Impact Analysis, Toxicity
		2015–2016	169 (71%)		Research cigarettes	

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Table 3 (*continued*)

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Higgins et al. (2018)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland			Secondary analysis of a multi-site, double-blind, within-participant laboratory assessment of responses to cigarettes varying in nicotine content, in which dependence severity was examined as a moderator of responses. Across populations, dependence severity did not moderate effects of nicotine content on measures of addiction liability or withdrawal, and had minimal effects on craving and topography.		Addiction, Behavior, Impact Analysis, Toxicity
Gaalema et al. (2017)	Cardiac rehab-ilitation patients in Vermont	2010–2014	1658 (27.2%)	Medical data extraction identifying patient characteristics associated with cardiac rehabilitation adherence. The highest-risk profile for non-adherence were patients younger than 65?years of age who currently smoked and had lower-SES.	Cigarettes	Behavior
Nayak et al. (2016)	U.S. National Sample	2014	1262 (49.3%)	Cross-sectional survey of a national probability sample found a higher proportion of dual users (cigarettes?+?ENDS) were college graduates versus cigarette-only smokers. Dual users were more likely to endorse intention to quit or to have made a quit attempt in the past year compared to cigarette-only smokers. Among dual users, those with a college degree had higher odds of intention to quit or of attempting to quit in the past year versus those with a high school education or less.	Cigarettes, ENDS	Addiction, Behavior
Shang et al. (2017)	Nationally represent-ative sample from 18 different countries	2008–2013	215, 655 (52.3%)	Person-level tobacco use data pooled from 18 countries was linked to warning label requirements in the same time period. Large pictorial warning labels (covering =50% of front and back of cigarette pack) were associated with lower smoking prevalence among adults with less than a secondary education or no education, but not among adults with at least a secondary education.	Cigarettes	Behavior, Impact Analysis, Communications
Lopez et al. (2018)	U.S. National Sample	2013–2014	12,848 (100%)	Cross-sectional study examining prevalence and correlates of current use of various tobacco products among non-pregnant women who completed Wave 1 of the PATH study. Overall prevalence was highest for cigarettes, and use of all alternative tobacco products was higher among current smokers vs. former or never-smokers. Socioeconomic variables were associated with current use of cigarettes and alternative tobacco products, with cigarette smoking being the strongest predictor of using e-cigarettes, hookah, and cigars.	Cigarettes, ENDS, Cigars, SLT, Snus, Pipes, Dissolv-ables, Hookah	Behavior
Roberts et al. (2016a)	U.S. National Sample	1995–2006	4766 (53%)	MIDUS[9] survey participants were followed up 10?years later to examine if late onset smoking[10] among African Americans is protective in terms of quitting and health outcomes compared to early-onset smoking. African American smokers had a later onset to smoking compared to white smokers. Late-onset African American smokers had lower quit rates compared to early-onset African American smokers, and African American smokers hazard rates for mortality were similar regardless of smoking onset.	Cigarettes	Behavior, Health Effects
Chivers et al. (2016)	Non-pregnant women recruited via Amazon Mechanical Turk	2014	800 (100%)	Online survey data were used to examine risk factors for e-cigarette use among women of reproductive age who were either daily smokers or never smokers. E-cigarette use was associated with greater nicotine dependence and attempts to quit among current smokers. E-cigarette use was associated with greater impulsivity and illegal drug use among never smokers.	Cigarettes, ENDS	Addiction, Behavior
Brasky et al. (2018)	Rural and Urban tobacco users in Ohio	2014–2016	1210 (44%)	Tobacco users in rural and urban counties in Ohio were interviewed to identify characteristics associated with use of tobacco products. Tobacco use behaviors and demographics differed by geographic region.	Cigarettes, SLT, ENDS	Behavior
Bergeria et al. (2018)	Pregnant and non-pregnant smokers in Vermont	2015–2016	109 (100%)	Experimental study examining whether disadvantaged women who reduced their cigarettes per day upon entering pregnancy were engaging in compensatory smoking relative to their non-smoking counterparts. Smoking topography, craving, and withdrawal did not differ between the two groups, but pregnant women had a significantly smaller CO boost after smoking and reported less pleasure from smoking relative to non-pregnant women.	Cigarettes	Addiction, Behavior, Health Effects

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Table 3 (*continued*)

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
White et al. (2014)	Pregnant women in Vermont	NR	349 (100%)	Secondary analysis examining educational attainment, pre-pregnancy smoking rate, and delay discounting as predictors of spontaneous quitting among pregnant smokers. Regression models adjusting for other predictors indicated that education and pre-pregnancy cigarettes per day were strong predictors of spontaneous quitting, whereas delay discounting predicted spontaneous quitting only among women with lower pre-pregnancy smoking rates.	Cigarettes	Addiction, Behavior
Vurbic et al. (2015)	U.S. National Sample	2007–2010	2477 (100%)	Examined effects of co-occurring obesity, smoking, and socioeconomic status on health outcomes among non-pregnant women who completed the NHANES[11] survey. Prevalence of co-occurring obesity and smoking increased as educational attainment decreased, and adverse health conditions (e.g., physical limitations, depression, high cholesterol) were more common among obese smokers vs. women who were obese or smokers alone.	Cigarettes	Health effects
Klein et al. (2015)	Rural smokers in Ohio	2013	296 (66%)	Experimental study comparing effectiveness of text only vs text?+?GHWs[12] embedded within cigarette advertisements. GHW messages attracted more attention and generated greater message recall than text-only labels.	Cigarettes	Impact Analysis, Communications
Lee et al. (2015)	FDA warning letters from advertising and labeling inspections	2014	718 warning letters	Cross-sectional study of neighborhood characteristics and retailer noncompliance with FDA advertising and regulation inspections. Regulated tobacco products were more likely to be stored behind the counter in African American and Hispanic/Latino neighborhoods, and single cigarettes were more available in neighborhoods with increased African Americans, young people, and individuals living below poverty.	Any tobacco	Impact Analysis, Marketing Influences
Roberts et al. (2015)	Rural and Urban stores	2014	199 stores (50% rural)	Observational study examined and compared external, point-of-sale exposure to tobacco marketing in rural vs urban areas. Promotions for e-cigarettes and advertising for menthol cigarettes, cigarillos, and cigars were more likely in urban, particularly highly disadvantaged, African American communities.	Cigarettes, ENDS, Cigars, Cigarillos, SLT	Impact Analysis, Marketing Influences
Cohn et al. (2018)	U.S. National Sample	2013–2014	NR	Used data from Wave 1 of the PATH study to examine correlates of menthol smoking among the top three cigarette brands, effects of menthol smoking on harm perceptions of one's usual brand cigarettes, and interactions with demographic variables. Menthol smokers were more likely to view their own brand as more harmful than other brands vs non-menthol smokers, with race and gender moderating the association between menthol brand preference and harm perceptions.	Cigarettes	Addiction, Behavior

[1] Shared superscripts indicate shared samples across studies.
[2] All of the studies described the gender/sex breakdown of their participants as male and/or female or as men and/or women. The studies did not address whether participants self-reported their assigned sex at birth and/or their gender identity at the time of the survey.
[3] National Survey on Drug Use and Health.
[4] Population Assessment of Tobacco and Health.
[5] Electronic Nicotine Delivery System.
[6] Smokeless tobacco.
[7] Not reported or could not be determined.
[8] Very Low Nicotine Content.
[9] National Survey of Midlife Development in the United States.
[10] Defined as regular smoking beginning at 18?years or beyond.
[11] National Health and Nutrition Examination Survey.
[12] Graphic Health Warnings.

Table 4
Characteristics of studies focused on Pregnant Women and Women of Reproductive Age.

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Higgins et al. (2017a)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Multi-site, double-blind, within-participant laboratory assessment of subjective and behavioral responses to cigarettes varying in nicotine content. Reducing the nicotine content of cigarettes reduced subjective and behavioral indicators of cigarette addiction liability across populations.	Research cigarettes	Addiction, Behavior, Impact Analysis, Toxicity
Arger et al., (2017)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Secondary analysis of a multi-site, double-blind, within-participant laboratory assessment of responses to cigarettes varying in nicotine content. Across populations, Satisfaction and Aversion subscale scores on the Modified Cigarette Evaluation Questionnaire predicted cigarette choices as measured using a concurrent-choice behavioral task.	Research cigarettes	Addiction, Behavior, Impact Analysis
Higgins et al. (2017a)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland	2014–2015	26 (77%)	Multi-site, double-blind, within-participant laboratory assessment of subjective and behavioral responses to cigarettes varying in nicotine content. Across populations, participants rated the VLNC[3] cigarettes lower in satisfaction and made fewer choices for these puffs relative to NNC cigarette puffs in concurrent choice testing. All cigarettes reduced withdrawal symptoms and none increased puff intensity.	Research cigarettes	Addiction, Behavior, Impact Analysis
Higgins et al. (2018)	Smokers with affective disorders, opioid dependence, and low SES women in Vermont, Rhode Island, and Maryland	2015–2016	169 (71%)	Secondary analysis of a multi-site, double-blind, within-participant laboratory assessment of responses to cigarettes varying in nicotine content, in which dependence severity was examined as a moderator of responses. Across populations, dependence severity did not moderate effects of nicotine content on measures of addiction liability or withdrawal, and had minimal effects on craving and topography.	Research cigarettes	Addiction, Behavior, Impact Analysis, Toxicity
Legro et al. (2014)	Women with polycystic ovary syndrome (PCOS) seeking fertility treatment	NR[4]	626 (100%)	Secondary analysis of a large randomized controlled study of infertility treatments in women with PCOS that examined whether smoking status was related to risk of infertility and response to infertility treatment. A subsample was used to validate self-reported smoking status with cotinine level. Current smoking was associated with a more severe phenotype at baseline and a lower treatment response in terms of metabolic and reproductive risk factors.	Cigarettes	Behavior, Health Effects
Cooper et al. (2018)	Pregnant smokers in Vermont	NR	93 (100%)	Analyzed effects of a randomized controlled trial of effects of abstinence-contingent vouchers on relationships between smoking, uterine blood flow and birth outcomes. No direct relationship between smoking and uterine artery hemodynamics was demonstrated. Volumetric flow was an independent contributor to birth weight and associated with fetal fat deposition; smoking was not independently associated with either outcome.	Cigarettes	Behavior, Health Effects
Lopez et al. (2018)	U.S. National Sample	2013–2014	12,848 (100%)	Cross-sectional study examining prevalence and correlates of current use of various tobacco products among non-pregnant women who completed Wave 1 of the PATH[5] study. Overall prevalence was highest for cigarettes, and use of all alternative tobacco products was higher among current smokers vs. former or never-smokers. Socioeconomic variables were associated with current use of cigarettes and alternative tobacco products, with cigarette smoking being the strongest predictor of using e-cigarettes, hookah, and cigars.	Cigarettes, ENDS[6], Cigars, SLT[7], Snus, Pipes, Dissolv-ables, Hookah	Behavior
Chivers et al. (2016)	Non-pregnant women recruited via Amazon Mechanical Turk	2014	800 (100%)	Online survey of non-pregnant women examining impulsivity and sociodemographic risk factors for e-cigarette use among cigarette smokers versus never-smokers. E-cigarette use among smokers was associated with increased nicotine dependence and attempts to quit smoking, whereas e-cigarette use among never-smokers was associated with greater impulsivity and illicit drug use.	Cigarettes, ENDS	Addiction, Behavior
Bergeria et al. (2018)	Pregnant and non-pregnant smokers in Vermont	2015–2016	109 (100%)	Experimental study examining whether women who reduced their cigarettes per day upon entering pregnancy were engaging in compensatory smoking relative to their non-smoking counterparts.	Cigarettes	Addiction, Behavior, Health Effects

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Table 4 (*continued*)

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
				Smoking topography, craving, and withdrawal did not differ between the two groups, but pregnant women had a significantly smaller CO boost after smoking and reported less pleasure from smoking relative to non-pregnant women.		
White et al. (2014)	Pregnant women in Vermont	NR	349 (100%)	Secondary analysis examining educational attainment, pre-pregnancy smoking rate, and delay discounting as predictors of spontaneous quitting among pregnant smokers. Regression models adjusting for other predictors indicated that education and pre-pregnancy cigarettes per day were strong predictors of spontaneous quitting, whereas delay discounting predicted spontaneous quitting only among women with lower pre-pregnancy smoking rates.	Cigarettes	Addiction, Behavior
Vurbic et al. (2015)	U.S. National Sample	2007–2010	2477 (100%)	Examined effects of co-occurring obesity, smoking, and socioeconomic status on health outcomes among non-pregnant women who completed the NHANES[8] survey. Prevalence of co-occurring obesity and smoking increased as educational attainment decreased, and adverse health conditions (e.g., physical limitations, depression, high cholesterol) were more common among obese smokers vs. women who were obese or smokers alone.	Cigarettes	Health Effects
Kurti et al. (2018a)	U.S. National Sample	2013–2015	9669 (100%)	Longitudinal study examining quit rates for various tobacco products among women who became pregnant across two waves of the PATH[8] study, as well as the impact of pregnancy versus other variables on quitting. Quit rates ranged between 54.0% for cigarettes to 96.8% for hookah, and pregnancy was significantly and independently associated with increased odds of quitting hookah, all tobacco, cigarettes, and e-cigarettes, but not cigars.	Cigarettes, ENDS, Cigars, Hookah	Addiction, Behavior
Kurti et al. (2018b)	U.S. National Sample	2013–2015	8137 (100%)	Longitudinal study examining prevalence and longitudinal trajectories of tobacco use patterns among women entering pregnancy, motherhood, or neither, across two waves of the PATH study. Regardless of pregnancy status, the most prevalent patterns of tobacco use were using cigarettes alone followed by dual use of cigarettes plus e-cigarettes. A majority of poly use involved cigarettes plus one or more additional products, with the most common transition being to drop the alternative tobacco product over time and smoke cigarettes exclusively.	Cigarettes, ENDS, Cigars, SLT, Snus, Pipes, Dissolvables, Hookah	Behavior, Health Effects
Kurti, et al. (2017)	U.S. National Sample	2013–2014	388 (100%)	Cross-sectional study examining prevalence and correlates of current use of various tobacco products among pregnant women who completed Wave 1 of the PATH study. Overall prevalence was highest for cigarettes, and use of all alternative tobacco products was higher among current smokers vs. former or never-smokers. Socioeconomic variables predicted current cigarette smoking, and current smoking and past-year illicit drug use in turn predicted use of e-cigarettes, hookah, and cigars.	Cigarettes, ENDS, Cigars, SLT, Snus, Pipes, Dissolv-ables, Hookah	Behavior
Higgins et al. (2017a)	U.S. National Sample	2005–2014	199,784 (100%)	Cross-sectional study examining whether use of full-flavor cigarettes was associated with increased nicotine dependence and smoking during pregnancy among women who completed the NSDUH[9] survey. Women using full-flavor cigarettes demonstrated increased odds of nicotine dependence relative to lower yield cigarettes, and using full-flavor cigarettes was associated with continuing to smoke during pregnancy.	Cigarettes	Addiction, Behavior
Heil et al. (2014)	Pregnant women in Vermont	2006–2009	107 (100%)	Examined the time course of changes in smoking between learning of pregnancy and initiating prenatal care among pregnant women enrolled in smoking cessation and relapse prevention trials. On average, women initiated prenatal care ~5?weeks after learning of pregnancy, during which time 22% of women became abstainers, 62% reduced their smoking, and 16% continued smoking. Changes in smoking occurred within two days upon learning of pregnancy, with few changes occurring after one week.	Cigarettes	Addiction, Behavior

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Table 4 (*continued*)

First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
White et al. (2015)	Pregnant women in Vermont	NR	349 (100%)	Comparison of two algorithms for identifying nonsystematic response sets in delay discounting data among pregnant smokers, as well as associations between participant characteristics and nonsystematic response sets. The algorithm recommended by Johnson and Bickel (2008) excluded fewer cases than conventional statistical model fit (R^2) and preserved order in the retained data. Correlates of providing nonsystematic data included younger age and lower educational attainment.	Cigarettes	Behavior
Higgins et al. (2017a)	Pregnant smokers in Vermont	NR	95 (100%)	Examined whether performance on a behavioral economic simulation task (CPT)[10] was associated with two well-validated predictors of smoking cessation (cigarettes per day, pre-pregnancy quit attempts) among pregnant women enrolled in an ongoing smoking cessation trial. Demand varied in correspondence to both predictors, and was more effective than both conventional variables in predicting whether women made a quit attempt during pregnancy.	Cigarettes	Addiction, Behavior
Taghavi et al. (2018a)	Pregnant Women in Vermont	NR	47 (100%)	Analyzed concentrations of urinary nicotine and metabolites among pregnant smokers enrolled in a smoking cessation trial during early and late pregnancy, as well as six months postpartum, to identify the extent and timing of changes in nicotine metabolism associated with pregnancy. Increases in nicotine metabolism start by 12?weeks gestation and continue as pregnancy progresses, contributing to reductions in the effectiveness of NRT during pregnancy.	Cigarettes	Addiction, Behavior, Toxicity, Health Effects
Taghavi et al. (2018b)	Pregnant smokers in Vermont	2006–2012	47 (100%)	Secondary analysis examining the utility of self-reported cigarettes per day (CPD), total nicotine equivalents (TNE), and urinary cotinine to estimate nicotine intake during pregnancy among pregnant women enrolled in a smoking cessation trial. CPD underestimated smoking due to under-reporting and/or higher intensity of smoking, and cotinine underestimated nicotine intake due to accelerated nicotine metabolism during pregnancy.	Cigarettes	Addiction, Behavior, Toxicity, Health Effects
Phillips et al. (2018)	Pregnant smokers in Vermont	NR[3]	388 (100%)	Secondary analysis of maternal and infant health outcomes among women who previously participated in smoking cessation trials. Among underweight/normal weight women, smoking was associated with preterm delivery and increased likelihood of NICU admissions, whereas smoking among overweight/obese women had no effect on gestational age at delivery, and infants were less likely to be admitted to the NICU.	Cigarettes	Health Effects
Vurbic et al. (2014)	Pregnant smokers in Vermont	NR	370 (100%)	Secondary analysis examining whether increases in breastfeeding associated with quitting smoking are moderated by maternal BMI among women previously enrolled in smoking cessation or relapse prevention trials. Smoking abstinence and normal/underweight were each associated with increased odds of breastfeeding, and the two interacted such that the relationship between smoking abstinence and breastfeeding was stronger among normal/underweight women than overweight/obese women.	Cigarettes	Behavior, Health Effects

[1] Shared superscripts indicate shared samples across studies.
[2] All of the studies described the gender/sex breakdown of their participants as male and/or female or as men and/or women. The studies did not address whether participants self-reported their assigned sex at birth and/or their gender identity at the time of the survey.
[3] Very Low Nicotine Content.
[4] Not reported or could not be determined.
[5] Population Assessment of Tobacco and Health.
[6] Electronic Nicotine Delivery System.
[7] Smokeless tobacco.
[8] National Health and Nutrition Examination Survey.
[9] National Survey on Drug Use and Health.
[10] Cigarette Purchase Task.

effects of using tobacco products, particularly cardiovascular and respiratory effects in clinical samples. Reports mainly focused on people with medical comorbidities rather than MHCs. Consistent with the studies in national samples discussed above (Higgins et al., 2016; White et al., 2016; Stanton et al., 2016; Spears et al., 2016; Miller et al., 2017), these studies showed a general pattern of smoking being associated with poorer health outcomes and poorer medical adherence (Gaalema et al., 2018a; Stokes et al., 2018). Moreover, one study using a longitudinal design demonstrated that smoking intensity and duration are associated with increased risk of diabetes mellitus in Black adults (White et al., 2018). Most studies in this domain focused on cigarette smoking, presenting a gap in understanding the potential risks of other tobacco use in populations with comorbid mental health or other medical conditions.

3.2.1. Summary/Conclusions

First, the observational studies reviewed in this section consistently documented that MHCs and medical comorbidities are risk factors for persistent smoking, with more recent studies indicating that these comorbidities may be risk factors for e-cigarette use as well. These findings underscore the need for studies examining responses to novel tobacco regulatory policies in populations with MHC and medical comorbid conditions. Second, results from the experimental studies reviewed in this section suggest that a nicotine reduction policy for cigarettes has the potential to reduce smoking among people with MHCs, although evidence of quitting is rare in these relatively short-duration studies. Future studies should examine whether access to non-combusted sources of nicotine can enhance the effects of a reduced-nicotine standard. Finally, studies are needed to address the gap in knowledge on how Communications and Marketing Influences may impact risk for tobacco use among people with MHCs and medical comorbidities.

3.3. Socioeconomic status

Perhaps the most well documented risk factor for cigarette smoking is low socioeconomic status (SES). Compared to the general population, people who live below the poverty line or have lower educational attainment are at increased risk for smoking, dependence, difficulties quitting, and smoking-related morbidity and mortality (U.S. Department of Health and Human Services, 2014; Jamal et al., 2018; Campaign for tobacco-free kids, 2015). Taking into account the tobacco use landscape of today and the regulatory landscape of the future, TCORS-supported investigators attempted to gain further insight into tobacco use in these populations and implications for tobacco regulation.

As noted above in the section addressing the Overall Search, 24 (35%) reports focused on lower-SES populations (Supplemental Table, Table 3). Each FDA scientific domain was addressed by one or more studies with most publications addressing the behavior domain (19, 79%), followed by addiction (11, 46%), impact analysis (7, 29%), health effects (3, 13%), toxicity (4, 17%), communications (2, 8%), and marketing influences (2, 8%). Most studies (14/24, 58%) addressed more than one domain. The greatest overlap was between the behavior and addiction domains, with the majority of studies (10/19, 53%) addressing behavior also addressing addiction, and all of those on addiction addressing behavior (10/10, 100%).

Ten of the 19 reports examining the behavior domain (Higgins et al., 2016; Roberts et al., 2017; White et al., 2016; Stanton et al., 2016; Higgins et al., 2017a; Gaalema et al., 2018a; Nayak et al., 2016; Shang et al., 2017; Lopez et al., 2018; Roberts et al., 2016a) used U.S. nationally-representative samples in providing current estimates on socioeconomic disparities in tobacco use. Two of those reports used the NSDUH to provide novel observations on commonalities and differences in socioeconomic risk factors for use of smokeless tobacco versus conventional cigarettes (White et al., 2016) and how use of higher-nicotine/tar-yield (full-flavor) cigarettes is overrepresented in socioeconomically disadvantaged populations and associated with increased risk for dependence (Higgins et al., 2017a). Similarly, data from Wave 1 of PATH demonstrated that use of mentholated cigarettes is also overrepresented in socioeconomically disadvantaged populations (Cohn et al., 2018). When examining tobacco use among women of reproductive age in Wave 1 of PATH, socioeconomic disadvantage predicted greater odds of using cigarettes or cigars but also lower odds of using e-cigarettes (Lopez et al., 2018), a pattern that is also discernible in other studies using nationally-representative (Nayak et al., 2016) and convenience samples (Chivers et al., 2016) and suggestive of the potential for e-cigarettes to exacerbate disparities in use of conventional cigarettes.

As discussed in the mental health and medical comorbidities section above, a series of four reports (Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c; Higgins et al., 2018) in the behavior and addictions domains demonstrated that reduced nicotine content cigarettes decreased the addiction potential of smoking in socioeconomically disadvantaged women without causing untoward levels of craving and withdrawal or generating compensatory smoking, the latter observation being highly relevant to the toxicity and health effects domains as well. TCORS researchers also laid important groundwork on how lower-SES status intersects with other vulnerabilities. For example, one of these reports demonstrated that socioeconomic risk factors intersect in a cumulative, summative manner with other co-occurring risk factors for cigarette smoking (Higgins et al., 2016). Two other reports (Roberts et al., 2017; Brasky et al., 2018) highlighted the intersection of SES with rural residence, a risk for tobacco use that is growing in importance in the U.S. and is discussed in greater detail below.

Nine (Higgins et al., 2017a; Gaalema et al., 2018a; Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c; Higgins et al., 2018; Nayak et al., 2016; Chivers et al., 2016; García et al., 2016) of the 11 reports addressing the addiction domain were addressed above. Two not mentioned focused on smoking during pregnancy among disadvantaged women, with one (Bergeria et al., 2018) offering evidence that pregnancy-related decreases in smoking rate are not associated with compensatory smoking, an encouraging finding relevant to toxicity and health effects domains. The second (White et al., 2014) demonstrated that impulsivity (delay discounting) and pre-pregnancy smoking rate interact in predicting quitting, with the former being a significant predictor among lighter smokers whereas the latter dominates among heavier smokers.

Four (Higgins et al., 2017b; Higgins et al., 2017c; Higgins et al., 2018; Bergeria et al., 2018) of the six studies focused on health effects and toxicity were discussed above. Among the two not yet addressed, one provided novel evidence that reductions in mortality risk associated with late-onset smoking are evident among White but not African American smokers and that this disparity is not an artifact of SES differences (Roberts et al., 2016a). The other provided seminal data demonstrating that the adverse health impacts of co-morbid smoking and obesity are disproportionately impacting socioeconomically disadvantaged women (Vurbic et al., 2015). Under the communications domain, two reports addressed response to graphic health warning labels among lower-SES populations, one in an experimental study (Klein et al., 2015) and the other using pooled survey data across 18 countries (Shang et al., 2017). Finally, two reports addressing marketing influences indicated that tobacco-marketing violations are heavily concentrated in socioeconomically disadvantaged communities (Lee et al., 2015; Roberts et al., 2015). Strengthening regulation against deliberate targeting of socioeconomically disadvantaged populations and implementing graphic warning labels on cigarette packaging, which have been found to be more effective among smokers with less education and lower income (Hitchman et al., 2012), would be productive steps towards reducing tobacco use disparities.

Table 5
Characteristics of studies focused on Race/Ethnicity.

Race/Ethnicity						
First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Higgins et al. (2016)	U.S. National Sample	2011–2013	114,426 (19%)	Three years of cross-sectional NSDUH[3] survey data were pooled to examine risk factors for current smoking. Age, gender, race/ethnicity, educational attainment, poverty, alcohol use disorders, substance use disorders and mental illness were all independently associated with smoking; effects of risk-factor combinations were typically summative.	Cigarettes	Behavior
White et al. (2016)	U.S. National Sample	2012	37,869 (51.9%)	Cross-sectional NSDUH study examined risk factors for current cigarette and SLT[4] use. Past year diagnosis of major depressive disorder and other demographic characteristics increased odds of smoking but not SLT use. Cigarette smoking was lower in Hispanic and Asian groups and higher in Native American and multiracial groups (vs Whites). The only race/ethnicity group more likely to use SLT than Whites were Native Americans.	Cigarettes, SLT	Behavior
Higgins et al. (2017a)	U.S. National Sample	2011–2013	114,426 (NR)[5]	Three years of cross-sectional NSDUH survey data were pooled to examine risk factors for smoking higher- vs. lower-nicotine yield cigarettes. Age, gender, race/ethnicity, educational attainment, poverty, substance use disorders and mental illness were independent risk factors for using higher-nicotine cigarettes, and use of higher-nicotine cigarettes increased risk for nicotine dependence.	Cigarettes	Addiction, Behavior
White et al. (2018)	African Americans in Mississippi	2000–2013	2991 (56.1%)	Longitudinal analysis of Jackson Heart Study participants examining associations between smoking and developing diabetes mellitus among those without diabetes at baseline. Heavy smoking (20 or more cigarettes per day) and pack-years were associated with increased risk of developing diabetes mellitus.	Cigarettes	Health Effects
Shang et al. (2017)	Nationally representative sample from 18 different countries	2008–2013	215, 655 (52.3%)	Data from 18 countries in the Global Adult Tobacco Survey were linked with warning label requirements from the MPOWER database. Prominent GHWs[6] were associated with a 10% lower cigarette smoking prevalence among less educated respondents. Results suggest that such warnings, if applied globally, could reduce health disparities associated with cigarette smoking.	Cigarettes	Impact Analysis, Communications
Lopez et al. (2018)	U.S. National sample of women of reproductive age	2013–2014	12,848 (100%)	Nationally representative, cross-sectional study of women of reproductive age examining prevalence and correlates of a wide range of tobacco products. Non-Hispanic Whites were more likely to use cigarettes and e-cigarettes vs. their counterparts in other race/ethnicity groups. However, cigar and hookah use were higher among all other race/ethnicity groups (non-Hispanic Black, Other, Hispanic) versus non-Hispanic Whites.	Cigarettes, ENDS[7], Cigars, SLT, Snus, Pipe, Dissolvable, Hookah	Behavior
Roberts et al. (2016a)	U.S. National Sample	1995–2006	4766 (53%)	Examined late onset smoking among African Americas using the National Survey of Midlife Development in the United States. Late-onset smoking was common among African Americans, but not protective against later cessation or mortality outcomes.	Cigarettes	Behavior, Health Effects
Chivers et al. (2016)	Non-pregnant women recruited via Amazon Mechanical Turk	2014	800 (100%)	Online survey of non-pregnant women examining impulsivity and sociodemographic risk factors for e-cigarette use among cigarette smokers versus never-smokers. E-cigarette use among smokers was associated with increased nicotine dependence and attempts to quit smoking, whereas e-cigarette use among never-smokers was associated with greater impulsivity and illicit drug use. Whites had higher odds of daily cigarette smoking vs other race/ethnicity groups.	Cigarettes, ENDS	Addiction, Behavior
Brasky et al. (2018)	Rural and Urban tobacco users in Ohio	2014–2016	1210 (44%)	Prospective cohort of users of combustible, SLT, and/or ENDS in rural and urban areas. SLT, ENDS, or dual product users were more likely to be white, ENDS and dual users were younger, and SLT users were almost all men and much more prevalent in rural than urban areas.	Cigarettes, ENDS, SLT	Addiction, Behavior

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Table 5 (*continued*)

Race/Ethnicity						
First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Lee et al. (2015)	FDA warning letters from advertising and labeling inspections	2014	718 warning letters	Cross-sectional study of neighborhood characteristics and retailer noncompliance with FDA advertising and regulation inspections. Regulated tobacco products were more likely to be stored behind the counter in African American and Hispanic/Latino neighborhoods, and single cigarettes were more available in neighborhoods with increased African Americans, young people, and individuals living below poverty.	Any tobacco	Impact Analysis, Marketing Influences
Roberts et al. (2015)	Rural and Urban stores	2014	199 stores (50% rural)	Observational study examined and compared external, point-of-sale exposure to tobacco marketing in rural vs urban areas. Promotions for e-cigarettes and advertising for menthol cigarettes, cigarillos, and cigars were more likely in urban, particularly highly disadvantaged, African American communities.	Cigarettes, ENDS, Cigars, Cigarillos, SLT	Impact Analysis, Marketing Influences
Sims et al. (2016)	African American cohort in Mississippi	2000–2004	4939 (63%)	Examined the relationship between perceived discrimination and cigarette smoking (along with other health behaviors such as sleep and dietary fat) in a large cohort of African Americans. Everyday discrimination was associated with higher levels of smoking in men and women. Burden of discrimination was associated with higher levels of smoking in women.	Cigarettes	Behavior
Leigh et al. (2017)	Cohort of Hispanic/Latinos in 4 U.S. metropolitan areas	2008–2011	1818 (57.4%)	Cohort study examining the relationship between cigarette smoking and cardiac structure and function conducted among Hispanic/Latinos. Results showed a dose-response relationship between intensity and duration of smoking and worsening measures of left and right ventricular structure and function.	Cigarettes	Behavior, Health Effects
Hall et al. (2016)	African American cohort in Mississippi	NR	3648 (NR)	Longitudinal study of large African American cohort (the Jackson Heart Study) evaluating the relation between cigarette smoking and rapid renal function (RRF). Current smokers had higher incidence of RRF decline than never smokers, even after controlling for other risk factors (i.e., sex, body mass index, diabetes, hypertension, cholesterol, physical activity, education, alcohol consumption, and prevalent cardiovascular disease).	Cigarettes	Health Effects
Garcia et al. (2016)	Vape shop employees in Los Angeles	2014	77 (14%)	Examined nicotine handling by vape shop customers and employees in African American, Hispanic, Korean and non-Hispanic White communities in Southern California. A majority of shop employees reported spills of e-liquid with nicotine and handling nicotine without safety equipment. This study highlighted the need for appropriate employee safety trainings in vape shops and equipment that could prevent accidental exposure among both customers and employees.	ENDS	Impact Analysis, Toxicity, Health Effects, Communications
Kamimura et al. (2018)	African American cohort in Mississippi	2000–2012	4129 (63%)	Examined cigarette smoking and cardiac dysfunction among a longitudinal cohort of African Americans who participated in the Jackson Heart Study. Cigarette smoking independently predicted later hospitalization for heart failure and worsening cardiac structure and function, even after controlling for coronary heart disease.	Cigarettes	Health Effects
Murphy et al. (2017)	1146 smokers (34% African American)	2016	Study 1, 795 (42.6%) Study 2, 651 (41.3%)	UGT2B10 (a protein-coding gene) activity was phenotyped by measuring the percentage of cotinine excreted as a glucuronide. Higher cotinine concentrations among African-American smokers were due to lower levels of UGT2B10-catalyzed cotinine glucuronidation.	Cigarettes	Addiction, Toxicity

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Table 5 (*continued*)

Race/Ethnicity						
First author (year)[1]	Sample description	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Choi et al. (2017)	African American and European American smokers and non-smokers	1999–2012	5040 (54.31%)	Cross-sectional study investigating the relationship between personality traits, cigarette smoking and nicotine dependence. Personality factors (e.g., higher neuroticism and agreeableness) had greater influence among African Americans versus European Americans, and a broader range of personality factors predicted higher levels of nicotine dependence among African Americans.	Cigarettes	Addiction
Baezconde-Garbanati et al. (2017)	Key opinion leaders and tobacco retailers in California	2016	10 focus groups (n?=?88)	Examined key opinion leaders and tobacco retailers from diverse race/ethnicity groups (African Americans, American Indians, Hispanic Americans, Korean and non-Hispanic Whites) in Los Angeles to assess retailers' compliance with regulatory processes. Results highlighted need for use of culturally and linguistically appropriate messaging when communicating with retailers.	Any tobacco	Impact Analysis, Marketing Influences
Cohn et al. (2018)	U.S. National Sample	2013–2014	NR	Used data from Wave 1 of the PATH[8] study to examine correlates of menthol smoking among the top three cigarette brands, effects of menthol smoking on harm perceptions of one's usual brand cigarettes, and interactions with demographic variables. Menthol smokers were more likely to view their own brand as more harmful than other brands vs non-menthol smokers, with race and gender moderating the association between menthol brand preference and harm perceptions.	Cigarettes	Addiction, Behavior
Garcia et al. (2016)	Vape shops in Los Angeles	2014	77 vape shops	Documented characteristics of vape shops via employee interviews and in-store observations. A majority of vape shops had advertisements for e-cigarettes and offered discounts. Vape shops in Hispanic communities were most likely to have ethnic-specific marketing material, and shops in Korean and White communities were most likely to have customer accessible free samples.	ENDS	Impact Analysis, Marketing Influences

[1] Shared superscripts indicate shared samples across studies.
[2] All of the studies described the gender/sex breakdown of their participants as male and/or female or as men and/or women. The studies did not address whether participants self-reported their assigned sex at birth and/or their gender identity at the time of the survey.
[3] National Survey on Drug Use and Health.
[4] Smokeless tobacco.
[5] Not reported or could not be determined.
[6] Graphic Health Warnings.
[7] Electronic Nicotine Delivery System.
[8] Population Assessment of Tobacco and Health.

Table 6
Characteristics of studies focused on Rural Residence.

Rural residence

First author (year)[1]	Sample [Description]	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Cepeda-Benito et al. (2018)	U.S. National Sample	2007–2014	303,311 (54%)	Eight years of cross-sectional NSDUH[3] survey data were pooled to predict adjusted and unadjusted smoking trends among men and women by rural vs urban residence. Prevalence declined in all groups except rural women, a pattern that remained when controlling for other risk factors.	Cigarettes	Behavior
Doogan et al. (2017)	U.S. National Sample	2007–2014	303,311 (54%)	Eight years of cross-sectional NSDUH survey data were pooled to predict adjusted and unadjusted smoking trends in rural vs urban areas. Prevalence declined faster in urban relative to rural areas, and this difference persisted even when controlling for other risk factors.	Cigarettes	Behavior
Roberts et al. (2017)	U.S. National Sample	2013–2014	32,320 (52%)	Compared prevalence of using traditional and emerging tobacco products using Wave 1 of the PATH[4] Study. Dual use of traditional tobacco products was more prevalent in rural than urban areas. Although emerging tobacco products were more prevalent among urban than rural subpopulations (e.g., e-cigarettes among men, hookah among women), rural/urban status did not reliably predict single or dual use of emerging tobacco products when adjusting for sociodemographic covariates.	Cigarettes, ENDS[5], Cigars, Cigarillos, SLT[6], Pipes, Hookah	Behavior
Nemeth et al. (2018)	Rural women in Ohio	2012–2013	401 (100%)	Cross-sectional data were used to examine risk factors for cigarette use. Younger age, greater depressive symptom severity, greater normative acceptance of smoking, and greater neighborhood cohesion increased the risks of smoking.	Cigarettes	Addiction, Behavior
Brasky et al. (2018)	Rural and Urban tobacco users in Ohio	2014–2016	1210 (44%)	Prospective cohort of users of combustible, SLT, and/or ENDS in rural and urban areas. SLT, ENDS, or dual product users were more likely to be white, ENDS and dual users were younger, and SLT users were almost all men and much more prevalent in rural than urban areas.	Cigarettes, ENDS, SLT	Addiction, Behavior
Klein et al. (2015)	Rural smokers in Ohio	2013	296 (66%)	Experimental study comparing effectiveness of text only vs text?+?GHWs[7] imbedded within cigarette advertisements. GHW messages attracted more attention and generated greater message recall than text-only labels.	Cigarettes	Impact Analysis
Roberts et al. (2015)	Rural and Urban stores	2014	199 stores (50% rural)	Observational study examined and compared external, point-of-sale exposure to tobacco marketing in rural vs urban areas. Promotions for e-cigarettes and advertising for menthol cigarettes, cigarillos, and cigars were more likely in urban, particularly highly disadvantaged, African American communities.	Cigarettes, ENDS, Cigars, Cigarillos, SLT	Impact Analysis, Marketing Influences
Roberts et al. (2016a)	U.S. National Sample	2012–2013	136,147	Pooled NSDUH cross-sectional surveys to track use of traditional tobacco products broken down by (a) US major geographical regions, (b) rural and urban divisions, and (c) poverty status. Smoking and SLT was more prevalent in rural than urban areas, but prevalence varied by US independently of income.	Cigarettes, Cigars, SLT, Pipes	Behavior
Curry et al. (2017)	Rural tobacco users in Ohio	2012–2013	240 (63%)	Longitudinal study among a convenience sample of smokers enrolled in cessation treatment. ENDS use was negatively associated with quitting success.	Cigarettes, ENDS	Addiction, Behavior
Doogan et al. (2018)	Rural and Urban tobacco users in Ohio	2014–2016	81 (62%)	Participants reported their tobacco purchases on a smartphone application. Average distance from home to a tobacco outlet was greater for rural relative to urban tobacco users. Among smokers, price promotions progressively and substantively increased purchasing quantities the further away tobacco outlets were from home. Conversely, promotion of SLT products increased purchasing quantity equally from near and far away outlets.	Cigarettes, SLT	Impact Analysis, Marketing Influences
Davison et al. (2016)	Rural smokers in Ohio	2013	296 (66%)	Survey study of a convenience sample of smokers reporting that over 70% of their sample endorsed ever consuming an energy drink, a prevalence rate that is substantively higher than those reported in energy drink studies using general community samples.	Cigarettes	Behavior
Klein et al. (2017)	Rural SLT users in Ohio	2013–2014	142 (0%)	Experimental study comparing effectiveness of text only vs text?+?GHWs imbedded within SLT products. GHW messages attracted more attention and generated greater message recall than text-only labels.	SLT	Impact Analysis, Communications

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Table 6 (*continued*)

First author (year)[1]	Sample [Description]	Data years	N (% female)[2]	Study description & main findings	Tobacco product	Scientific domains
Rural residence						
Roberts et al. (2016a)	Rural smokers in Ohio	2013	295 (66%)	Experimental study comparing effectiveness of text only vs text? + ?GHWs imbedded within cigarette advertisements. Beliefs about smoking risks, quitting history, and cigarettes per day did not correlate with the relative time smokers spent viewing cigarette advertisement GHWs, and age was negatively associated to the attention paid to GHWs.	Cigarettes	Addiction, Impact Analysis, Communications

[1] Shared superscripts indicate shared samples across studies.

[2] All of the studies described the gender/sex breakdown of their participants as male and/or female or as men and/or women. The studies did not address whether participants self-reported their assigned sex at birth and/or their gender identity at the time of the survey.

[3] National Survey on Drug Use and Health.

[4] Population Assessment of Tobacco and Health.

[5] Electronic Nicotine Delivery System.

[6] Smokeless tobacco.

[7] Graphic Health Warnings.

3.3.1. Summary/Conclusions

These reports document strong associations between SES and tobacco use patterns. Continued research focusing on tobacco prevention or interventions for lower SES populations could have important population-level effects on smoking. Several findings highlighted tobacco marketing influences and violations concentrated in poorer communities, strategies that may counteract tobacco control policies. In addition, educational campaigns for tobacco control and regulatory policies should be mindful of SES to maximize effectiveness. Lastly, SES intersects with most of the other major risk factors for tobacco use, including mental health/medical comorbidities and rural/urban geographies, and thus needs to be considered whenever developing tobacco control and regulatory policies to reduce tobacco use.

3.4. Pregnant women and women of reproductive age

As discussed in the Introduction, smoking rates among women have decreased at a slower rate than among men and have increased among socioeconomically disadvantaged women (Schroeder & Koh, 2014; Higgins & Chilcoat, 2009; Chilcoat, 2009). Cigarette smoking and other tobacco use among women of reproductive age is of particular concern due to the potential for serious adverse effects on maternal and infant health should the user become pregnant (Cnattingius, 2004; Dietz et al., 2010; Pauly & Slotkin, 2008; CDC, 2018).

Among the 22 (31%) reports examining tobacco use among women of reproductive age (Supplemental Table, Table 5), 17 (77%) focused exclusively on cigarette smoking and five (23%) on the use of multiple tobacco products. The reports addressed topics relevant to five of the seven scientific domains, with all but one report listed under multiple domains (Supplemental Table). The domain under which the largest number of reports was listed was behavior (19, 86%), followed by addiction (14, 64%), health effects (6, 27%), toxicity (7, 32%), and impact analysis (4, 18%). No reports were listed under communications or marketing.

Most of the reports (77%) listed under behavior were also listed under addiction and in turn all of those listed under addiction were listed under behavior. Five reports (Lopez et al., 2018; Kurti et al., 2018a; Kurti et al., 2018b; Kurti et al., 2017; Higgins et al., 2017d) addressed knowledge gaps on prevalence of current use of conventional cigarettes and a broad range of other tobacco products among U.S. nationally-representative samples. Two of the studies provide parallel, cross-sectional prevalence estimates on use of conventional and emerging tobacco products using data from Wave 1 (2013–2014) of PATH, with one focusing on non-pregnant women of reproductive age (Lopez et al., 2018) and the other pregnant women (Kurti et al., 2017). While CDC regularly reports on prevalence of smoking during pregnancy under its Pregnancy Risk Assessment Monitoring System (PRAMS), only cigarette smoking is tracked and the samples are not nationally representative (CDC - PRAMStat Data Portal - pregnancy risk assessment monitoring system - reproductive health, 2018). Those two parallel studies demonstrated relatively high levels of current tobacco use, especially combusted tobacco use with 20.1%, 4.9%, and 6.5% of non-pregnant women and 13.8%, 2.3%, and 2.5% of pregnant women currently using cigarettes, cigars, and hookah, respectively. Current use of e-cigarettes was 5.9% and 4.9% among non-pregnant and pregnant women, respectively. Those studies provided an excellent framework for two follow-up longitudinal studies (Lopez et al., 2018; Kurti et al., 2018b) in nationally-representative samples assessing use patterns over time including cessation rates during pregnancy. Among non-pregnant current users in Wave 1 who were pregnant in Wave 2, only 54% of cigarette smokers had ceased use compared to 96.8% of hookah smokers, 87.3% of cigar smokers, and 79.6% of e-cigarette users. The fifth study provides novel cross-sectional data underscoring that use of high nicotine-yield cigarettes among women of reproductive age predicts tobacco dependence and smoking through pregnancy (Higgins et al., 2017d).

Those five reports utilizing nationally-representative samples are complemented by studies with convenience samples (a) providing seminal data on the timing of smoking cessation during pregnancy (Heil et al., 2014), (b) using socioeconomic characteristics and innovative behavioral-economic tasks to predict smoking cessation and e-cigarette use (Chivers et al., 2016; White et al., 2014; White et al., 2015; Higgins et al., 2017e), and (c) providing new knowledge on the time-course of pregnancy-related changes in nicotine metabolism (Taghavi et al., 2018a; Taghavi et al., 2018b) and experimental evidence suggesting that those changes do not promote compensatory smoking (Bergeria et al., 2018).

Another group of reports (Higgins et al., 2017b; Arger et al., 2017; Higgins et al., 2017c; Higgins et al., 2018) under the behavior, addiction, and impact analysis domains provided experimental evidence that VLNCs decrease the addiction potential of cigarette smoking among women of reproductive age, complementing results on VLNCs in other populations (Donny et al., 2015).

Other studies under the health effects domain used nationally-representative and convenience samples to demonstrate that compared to either condition alone, co-morbid cigarette smoking and obesity is associated with socioeconomic disadvantage and numerous increases in adverse health biomarkers and outcomes (Vurbic et al., 2015; Phillips et al., 2018; Vurbic et al., 2014). Other studies in this domain provided insights into mechanisms by which smoking during pregnancy alters fetal growth (Cooper et al., 2018), and persistence of cigarette smoking during fertility treatment (Legro et al., 2014), a highly risky period to be smoking.

3.4.1. Summary/Conclusions

These 22 reports addressing five of the seven FDA domains demonstrate considerable breadth in the TCORS research conducted with pregnant women and women of reproductive age. Included was much-needed prevalence data on current use and pregnancy-related cessation in national samples. Strong evidence of relatively high rates and persistent cigarette smoking was evident across reports. More encouraging are the data from experimental studies indicating that reducing the nicotine content of cigarettes to very low levels decreases the addiction potential of smoking in this population. The studies provided additional new knowledge on timing of cessation during pregnancy, time-course of pregnancy-related changes in nicotine metabolism, the potential of novel methods from behavioral economics to predict product preference, and how the already considerable contributions of smoking to health disparities among women are exacerbated by co-occurring obesity. A notable gap in this set of studies is the absence of any reports addressing the scientific domains of communications and marketing of tobacco products to women of reproductive age.

3.5. Race and ethnicity

Disparities in vulnerability to tobacco use associated with race and ethnicity are of considerable concern to tobacco regulators. Among the 21 (29%) reports examining race/ethnicity (Supplemental Table, Table 5), 10 (48%) focused on the domain of behavior, six (29%) each on addiction, health effects, and impact analysis, four (19%) on marketing influences, and two (10%) each on toxicity and communications.

Reports addressing the behavior domain (Higgins et al., 2016; White et al., 2016; Higgins et al., 2017a; Lopez et al., 2018; Roberts et al., 2016a; Chivers et al., 2016; Brasky et al., 2018; Sims et al., 2016; Leigh et al., 2017; Cohn et al., 2018) provided a broad range of converging evidence including six studies in U.S. nationally-representative samples (Higgins et al., 2016; White et al., 2016; Higgins et al., 2017a; Lopez et al., 2018; Roberts et al., 2016a; Cohn et al., 2018) indicating that certain race/ethnicity minority groups are more vulnerable to combustible tobacco use and face unique risk factors for tobacco use including discrimination. For example, analyses of nationally-representative samples in the NSDUH demonstrated that prevalence of cigarette smoking is greater in Native American and multiracial groups, compared to non-Hispanic Whites (White et al., 2016). Another study using PATH demonstrated that use of cigars is greater in several race/ethnicity groups (non-Hispanic Black, Hispanic/Latino, Other) compared to Non-Hispanic Whites, while the opposite is true for e-cigarette use (Lopez et al., 2018). Another study using a cohort sample of rural tobacco users showed that users of combustible tobacco were more likely to be non-White compared to users of smokeless tobacco, e-cigarettes and dual products (Brasky et al., 2018). Lastly, a cohort study (Jackson Heart Study) demonstrated that discrimination is associated with greater odds of smoking among African Americans (Sims et al., 2016).

The reports addressing health effects (Roberts et al., 2016a; Hall et al., 2016; Garcia et al., 2016; Kamimura et al., 2018; Murphy et al., 2017) document substantial risk between use of combustible tobacco products and later chronic disease and mortality in African American and Hispanic/Latino groups using nationally-representative (Roberts et al., 2016a) and cohort samples (White et al., 2018; Leigh et al., 2017; Hall et al., 2016; Garcia et al., 2016; Kamimura et al., 2018). Notably, the study in the nationally-representative sample (National Survey of Midlife Development in the U.S.) noted that late-onset smoking predicted reduced smoking-related health risk in Whites but not African Americans, and prospective cohort studies of African Americans demonstrated that cigarette smoking was independently associated with renal dysfunction (Hall et al., 2016), later diabetes risk (White et al., 2018), and hospitalization for coronary heart disease (Kamimura et al., 2018). A cohort study of Hispanic/Latinos (Leigh et al., 2017) documented a dose-response relationship between intensity and duration of smoking with worsening heart structure and function.

Reports discussing the addiction domain (Higgins et al., 2017a; Chivers et al., 2016; Brasky et al., 2018; Murphy et al., 2017; Choi et al., 2017; Cohn et al., 2018) collectively show that racial/ethnic minorities have unique characteristics that may place them at increased risk for nicotine dependence. For example, a study in a U.S. nationally-representative sample noted that minority race/ethnicity status was associated with greater use of full-flavor cigarettes and use of full-flavor cigarettes was associated with greater tobacco dependence (Higgins et al., 2017a). As another example, a secondary analysis of data from participants in clinical trials on reduced nicotine content cigarettes revealed that the well-established higher cotinine concentrations among African-American compared to other ethnic/racial smokers is attributable to a genetic variation among the former (i.e., a UGT2B10 splice variant resulting in lower levels of UGT2B10-catalyzed cotinine glucuronidation) (Murphy et al., 2017).

Reports addressing marketing influences (Lee et al., 2015; Roberts et al., 2015; Baezconde-Garbanti et al., 2017; García et al., 2016) demonstrated that compliance with FDA regulations was associated in various ways with racial/ethnic neighborhood composition, an understudied topic. For example, examination of 7 months' worth of FDA warning letters (718 letters) for advertising and labeling violations demonstrated that retailer noncompliance with FDA bans on self-service displays, selling of single cigarettes, false or mislabeled products, vending machines, flavored cigarettes and free samples was significantly associated with racial/ethnic neighborhood composition.

Reports addressing the impact analysis domain (Shang et al., 2017; Lee et al., 2015; Roberts et al., 2015; Garcia et al., 2016; Baezconde-Garbanti et al., 2017; García et al., 2016), including two that also addressed communications (Shang et al., 2017; Garcia et al., 2016) and one that addressed toxicity (Garcia et al., 2016), attributed tobacco use disparities partly to lack of regulation compliance and/or tobacco industry targeting in racial/ethnic communities. One study of 18 racially and ethnically diverse countries concluded that prominent pictorial warning labels could have an impact in reducing smoking-related health disparities (Shang et al., 2017). Studies of vape shops in diverse neighborhoods underscored a need for regulations on handling of nicotine by customers and employees to address frequent spills and

limited safety training/equipment (Garcia et al., 2016). These studies also documented differences in marketing practices across ethnic communities (García et al., 2016).

3.5.1. Summary/Conclusions

Most studies reviewed in this section focused on larger racial/ethnic groups (African Americans, Hispanics/Latinos and Non-Hispanic Whites) with little detailed data reported, for example, on Asian/Pacific Islander or American Indian groups. Included papers highlight the need for stronger regulatory enforcement that will help reduce disparities associated with marketing to vulnerable populations. Targeted approaches to FDA retailer inspections and culturally and linguistically appropriate educational campaigns for retailers are also recommended. Moreover, studies point to greater implementation of regulations as a potential way to lower cigarette smoking prevalence in racial/ethnic communities. Gaps found in the research suggest the need for disaggregating data for Asian populations and to increase research available on American Indians/Alaska Native populations.

3.6. Rural populations

Those living in rural areas of the U.S. are at increased risk of being cigarette smokers and/or smokeless tobacco (SLT) users (Bolin et al., 2015; Hartley, 2004). Thirteen (18%) of the 71 reports in this review investigated rural populations across five of the seven scientific domains prioritized by FDA, although none addressed toxicity or health effects (Supplemental Table, Table 6).

Four of these reports used nationally-representative samples to provide a more detailed and nuanced characterization of tobacco use disparities by rural/urban residence (Cepeda-Benito et al., 2018; Doogan et al., 2017; Roberts et al., 2017; Curry et al., 2017). Two studies examined trends across multiple years (2007–14) of NSDUH revealing that cigarette smoking prevalence is declining at a slower rate in rural than urban areas and that well-established socioeconomic, psychosocial, and demographic risk factors no longer fully account for these differences (Cepeda-Benito et al., 2018; Doogan et al., 2017). Additionally, one of those studies indicated that a disproportionate degree of this variance in rural-urban smoking trends is attributable to unchanging smoking trends over time in rural women contrasted against a steep decline among urban women (Cepeda-Benito et al., 2018). The third study pooled NSDUH data from 2012 to 2013 demonstrating that while rural-urban smoking disparities in use of conventional tobacco products are discernible throughout the U.S., the greatest differences are seen in the South Census region, especially the South Atlantic division (Roberts et al., 2016b). Lastly, the fourth in this series of studies used data from Wave 1 (2013–2014) of PATH to broaden investigation of rural-urban disparities in tobacco use to include emerging tobacco products (Roberts et al., 2017). Consistent with the other studies, greater cigarette smoking and smokeless tobacco use in rural than urban areas including dual use was well documented, but no differences in e-cigarette use were noted, and there was greater urban than rural use of cigarillos and hookah, as well as more dual use involving emerging products.

The remaining studies (Nemeth et al., 2018; Brasky et al., 2018; Klein et al., 2015; Roberts et al., 2015; Curry et al., 2017; Doogan et al., 2018; Davison et al., 2016; Klein et al., 2017; Roberts et al., 2016c) addressed various tobacco regulatory science topics using convenience or cohort samples, the largest of which was a prospective cohort study of rural and urban Ohio residents who used conventional tobacco products and/or e-cigarettes (Brasky et al., 2018). Compared to urban residents, rural residents reported heavier and longer duration tobacco use histories, as well as lower interest in quitting, although no differences in nicotine dependence or past-year quit attempts were noted (Brasky et al., 2018).

Two studies (Roberts et al., 2015; Doogan et al., 2018) examining tobacco marketing revealed patterns consistent with rural-urban differences in tobacco use patterns noted above. Point-of-sale marketing of emerging products (cigarillos, e-cigarettes) was greater in urban than rural settings (Roberts et al., 2015) and the influence of cigarette price promotions on purchasing quantities increased as an orderly function of the distance between home and tobacco outlets (Doogan et al., 2018). Purchase of smokeless tobacco products also increased in relation to price promotions; that relation did not increase by travel distance but would nevertheless be expected to disproportionately impact rural residents corresponding to their greater prevalence of smokeless tobacco use.

Three studies (Klein et al., 2015; Klein et al., 2017; Roberts et al., 2016c) compared reactivity to tobacco text- vs graphic-health warnings (GHW). Given that rural residents are uniquely targeted by tobacco marketing (Pokhrel et al., 2009) and inadequately exposed to tobacco health communications (Balamurugan et al., 2007), it is noteworthy that GHWs were more impactful than text-only warnings in these rural samples (Klein et al., 2015; Klein et al., 2017), although that effect may dissipate in older age (Roberts et al., 2016c). Three other reports with small, convenience samples of rural smokers found a negative correlation between post-treatment e-cigarette use and smoking abstinence (Curry et al., 2017), that neighborhood cohesion and normative acceptance of smoking predicted greater smoking among rural women (Nemeth et al., 2018), and that energy-drink consumption among rural smokers was higher than previously reported (Davison et al., 2016).

3.6.1. Summary/Conclusions

The studies in nationally representative samples revealed reliable, increasing rural-urban disparities that go beyond what can be accounted for by well-established sociodemographic and psychosocial risk factors for smoking. The evidence clearly suggests that tobacco policies and regulations often credited with reducing smoking prevalence in the U.S. have been less effective in rural than urban settings. Greater investigation of whether tobacco control and regulatory policies and interventions may have been differentially implemented, enforced, or appropriately tailored to the needs of rural populations is clearly warranted. The absence of any studies examining rural-urban disparities in toxin exposure and tobacco-related adverse health effects underscores another important gap to address going forward. The proverbial “more research is needed” may sound hollow but definitely fits this growing vulnerability of rural residence to cigarette smoking and smokeless tobacco use.

3.7. Active military and veterans

Smoking rates among U.S. active military are considerably higher than in the general population (Department of Veterans Affairs, Veterans Health Administration, 2011). Nearly one-quarter (24%) of active duty military personnel are current cigarette smokers, with the highest prevalence in the Marine Corps (30.8%), followed by Army (26.7%), Navy (24.4%), and Air Force (16.7%). Studies suggest that a positive tobacco culture in the military drives consumption (Haddock et al., 2009; Nelson et al., 2009; Poston et al., 2008), and that current dangers in the field may discount the salience of longer-term potential adverse health impacts of tobacco use (Poston et al., 2008). Among smokers who quit, military deployment is strongly associated with relapse, particularly prolonged deployments, multiple deployments, or combat exposure (Smith et al., 2008). Rates of current tobacco use among U.S. veterans also exceed those in the general population (Kirby et al., 2008; McClernon et al., 2013; Odani et al., 2018).

Among the two reports (3%) identified in this topic area (Hefner et al., 2016; Valentine et al., 2018), both used convenience samples of veterans to conduct studies relevant to the domains of addiction and behavior, with one report (Valentine et al., 2018) also addressing toxicity (Supplemental Table). Because there were only two studies on this population, details are summarized without an accompanying table. Both studies examined e-cigarette use among those with co-

morbid psychiatric conditions, documenting awareness and use of e-cigarettes. There was no evidence in either study of e-cigarettes facilitating greater smoking cessation, although reductions in cigarettes per day and breath carbon monoxide were observed in an open trial of experimenter-provided e-cigarettes (Valentine et al., 2018). The authors recommended greater study of e-cigarette use among veterans with comorbid psychiatric conditions as a harm-reduction strategy.

3.7.1. Summary/Conclusions

Clearly there is a need for greater tobacco regulatory science research with the active military and veterans. In particular, further research is needed on the potential use of e-cigarettes or other non-combusted tobacco products as a harm-reduction strategy within this population.

3.8. Sexual and gender minority populations

Smoking prevalence among sexual and gender minority populations in the U.S. is considerably higher than the general population (CDC, 2019). More information is available on sexual (lesbian, gay, and bisexual adults, LGB) than gender (T) minorities. In a 2016 nationally-representative sample of U.S. adults, prevalence of cigarette smoking was estimated to be 1.34-fold greater among LGB (20.5%) than heterosexual individuals (15.3%) (Jamal et al., 2018). This has been attributed to higher levels of daily stress related to social stigma in addition to aggressive marketing of tobacco to these populations (Brewster & Tillman, 2012; Panel TU and DG, 2008). The higher combusted tobacco use among LGBT individuals contributes to increased smoking-attributable respiratory illnesses compared to the general population (Blosnich et al., 2011).

Of the two reports (3%) examining LGBT tobacco use (Brasky et al., 2018; Nayak et al., 2017), both addressed behavior and one (Nayak et al., 2017) addiction (Supplemental Table). Again, with only two studies on this population, details are summarized without an accompanying table. One report examined use and harm perceptions of novel and alternative tobacco products among LGB adults in a nationally-representative survey (Nayak et al., 2017). After controlling for potential confounders, LGB adults were 1.5 times more likely to have ever used e-cigarettes (95% CI 1.2–1.9) and 1.9 times more likely to have ever used hookah (95% CI 1.5–2.4) compared to heterosexual adults. A somewhat lower percentage of LGB than heterosexual adults believed that second-hand exposure to e-cig vapor was harmful (16.7% vs. 19.2%) and reported that they did not know of any harm from exposure to e-cig vapor (35.1% vs. 39.8%). The other report simply noted what proportion of tobacco users included in a longitudinal cohort of urban and rural tobacco users were from LGBT groups, and the proportion of combustible, smokeless, ENDS, and dual users they comprised (Brasky et al., 2018).

3.8.1. Summary/Conclusions

There is a clear need for greater tobacco regulatory research with sexual and gender minority populations. Greater prevalence of tobacco use and associated harms is well documented, but substantial gaps in knowledge remain regarding how to reduce such disparities.

4. Overall summary and conclusions

Summaries and conclusions specific to each of the seven vulnerable populations were discussed in the Results section and are not repeated here. Overall, this review demonstrates a substantive, multidisciplinary scientific contribution to advancing knowledge on tobacco use and its impact among adult vulnerable populations from Phase 1 of the TCORS initiative, which is a critically important initial step towards developing and implementing policies that reduce the burden of tobacco use on public health. This contribution includes 71 publications in peer-reviewed journals that are reasonably well distributed across the seven vulnerable populations prioritized in the FDA TCORS RFAs save for the strikingly low number of studies with active military/veterans and sexual and gender minority populations, a knowledge gap that should be addressed going forward.

The distribution of reports across the seven scientific domains prioritized in those same FDA TCORS RFAs shows that the greatest research attention went to behavior and addiction, intermediate levels to health effects, toxicity, and impact analysis, and relatively little to communications and marketing influences. Devoting considerable attention to behavior, addiction, health effects, and toxicity in getting the TCORS and tobacco regulatory science more generally off the ground is certainly understandable as those domains represent the raison d'être for the CTP (i.e., tobacco use, development of chronic use and addiction, and the resultant adverse impacts on health). The initial evidence summarized above noting that socioeconomically disadvantaged populations respond differently to educational and warning materials than more advantaged populations and that vulnerable populations are targeted in tobacco advertising and other marketing campaigns underscores the need to address this gap in research on communications and marketing influences in future TCORS efforts. Possible disparities in tobacco control and regulatory implementation and enforcement in socioeconomically disadvantaged neighborhoods and rural regions also calls for greater attention.

We have attempted to underscore how the initial phase of TCORS support has advanced knowledge on tobacco use in vulnerable populations in the Summary and Conclusion sections specific to each of the populations included above. Here we further emphasize three of those advances that we deem particularly noteworthy. First, included among the 71 publications identified in this review is an impressive set of reports describing epidemiological studies in nationally-representative samples that characterize current prevalence rates and use patterns of conventional and emerging tobacco products among vulnerable populations, basic information necessary for conducting evidence-based regulation. The epidemiological studies investigating rural populations and women of reproductive age are particularly notable for the programmatic approach taken across reports. Such information will be critically important for discerning progress or the lack thereof with regard to reducing the burden of tobacco use in these populations. Second, the subset of experimental studies on VLNCs among vulnerable populations is notable for the detailed examination of the potential of a national policy that caps cigarette nicotine content at minimally-addictive levels to positively impact those smokers who are most at risk for smoking and associated adverse health impacts. Such careful attention to potential policy impacts in vulnerable populations is laudable and we believe an important component of an evidence-based approach to tobacco regulation going forward. As a third and final example, the studies included in this review clearly demonstrate the pervasive intersection of vulnerabilities for tobacco use (e.g., socioeconomic status, race/ethnicity, rural vs. urban residence, and co-morbid medical and mental health conditions), which is an understudied but important aspect of understanding disparities in tobacco use that will be important to consider in developing more effective tobacco regulatory policies and when conducting associated impact analyses (Leventhal et al., 2019).

A notable limitation is that by attending exclusively to TCORS funded research this review inevitably ignored studies potentially relevant to tobacco regulatory science and vulnerable populations that were supported through other mechanisms. While the TCORS represented the mechanism by which TRSP kicked off development of a research literature explicitly focused on tobacco regulatory science, it has expanded its research portfolio to now include an assortment of other research and career development funding mechanisms and projects (Office of Disease Prevention, National Institute of Health, 2019). While the TCORS continue to represent a centerpiece of research in this relatively nascent topic area, staying apprised of developments in tobacco regulatory science research going forward will necessitate inclusion of research supported through these more recent mechanisms as well.

There is little question that the TCORS effort and the field of tobacco regulatory science more generally are still early in their development with many knowledge gaps remaining to be addressed. However, this review provides compelling evidence that the initial phase of TCORS support has succeeded in generating a body of rigorous multidisciplinary research on tobacco use in adult vulnerable populations relevant to the 2009 Tobacco Control Act identifying, for example, subgroups of the US population who are particularly vulnerable to tobacco use, less successful at quitting cigarette smoking, and could benefit significantly from targeted communication and potential regulatory policies such as reducing nicotine levels in cigarettes. This body of work is complemented by additional TCORS-supported research in youth and young adults (Perry et al., in press) and will continue to expand in Phase 2 of TCORS and with the growth of tobacco regulatory science research funded by other mechanisms. This body of work provides a solid foundation to build upon in the next phase of TCORS research and expansion of TRSP research generally. While we see a clear need for addressing knowledge gaps as noted above, we see no need for a qualitative change in the type or scope of tobacco regulatory science research with vulnerable populations research going forward. Important to recognize is that while focused largely on tobacco use in vulnerable populations in the U.S., we anticipate that this unprecedented investment in tobacco regulatory science that the TCORS and other TRSP-supported mechanisms represent will also be of considerable value to global regulatory efforts to reduce the burden of tobacco use in vulnerable populations. Similarly, while focused on tobacco regulatory science, the research effort examined in this review has generated new knowledge on tobacco use in vulnerable populations that should also be of value to tobacco control efforts with these same populations.

Conflicts of interest

None to declare.

Funding

This project was supported in part by Tobacco Centers of Regulatory Science (TCORS) award U54DA036114 from the National Institute on Drug Abuse (NIDA) and Food and Drug Administration (FDA), TCORS award U54DA031659 from NIDA and FDA, TCORS award P50CA180908 from the National Cancer Institute (NCI) and FDA, TCORS award P50HL120163 from the National Heart, Lung, and Blood Institute and FDA, Center for Evaluation and Coordination of Training and Research award U54CA189222 from the NCI and FDA, TCORS Award P50-DA-036107 from NIDA and FDA, TCORS award P50CA180905 from NCI and FDA, Centers of Biomedical Research Excellence P20GM103644 award from the National Institute of General Medical Sciences, and Research awards R01HD075669 from the National Institute of Child Health and Human Development (NICHD) and Centers for Disease Control and Prevention and R01HD078332 from NICHD. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.04.024.

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