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Global regional economic and tobacco regulatory factors influence smoking cessation outcomes in the multinational EAGLES randomized controlled trial

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ABSTRACT

Introduction We previously reported global regional differences in smoking cessation outcomes, with smokers of United States origin having lower quit rates than smokers from some other countries. This *post hoc* analysis examined global regional differences in individual- and country-level epidemiologic, economic, and tobacco regulatory factors that may affect cessation outcomes.

Methods EAGLES (NCT01456936) was a randomized controlled trial that evaluated first-line cessation medications and placebo in 8144 smokers from 16 countries across seven regions. Generalized linear and stepwise logistic regression models that considered pharmacotherapy treatment, psychiatric diagnoses, traditional individual-level predictors (e.g., demographic and smoking characteristics), and country-specific smoking prevalence rates, gross domestic product (GDP) *per capita*, relative cigarette cost, and WHO-derived MPOWER scores were used to predict 7-day point prevalence abstinence at the end of treatment.

Results In addition to several traditional predictors, three of four country-level variables predicted short-term abstinence: GDP (0.54 [95% CI 0.47, 0.63]), cigarette relative income price (0.62 [0.53, 0.72]), and MPOWER score (1.03 [1.01, 1.06]). Quit rates varied across regions (22.0% in Australasia to 55.9% in Mexico). With North America (United States and Canada) as the referent, the likelihood of achieving short-term abstinence was significantly higher in Western Europe (OR 1.4 [95% CI 1.14, 1.61]), but significantly lower in Eastern Europe (0.39 [0.22, 0.69]) and South America (0.17 [0.08, 0.35]).

Conclusions Increased tobacco regulation, more affordable cigarette pricing, and lower GDP were associated with enhanced quitting among smokers in the EAGLES trial. Geographic region was also a significant independent predictor.

WHAT THIS STUDY ADDS

WHAT IS ALREADY KNOWN ON THIS TOPIC

Population-based studies examining individual and country-level factors associated with abstinence after a quit attempt have found wide variation across countries and inconsistent support of the "hardening hypothesis," which posits that smokers in countries with low smoking prevalence will possess characteristics that make it harder to quit. However, those studies focused on high-income countries in North America, the European Union, and Australia and did not examine a standardized response to the first-line smoking cessation medications.

WHAT THIS STUDY ADDS

EAGLES is the largest, randomized, placebo-controlled trial of cessation medications ever conducted that enrolled smokers with and without psychiatric disorders in 16 high- and middle-income countries across five continents. The authors found that in addition to several traditional individual-level factors predicting short-term cessation success, increased tobacco regulation, lower relative cigarette cost, and lower GDP were associated with enhanced quitting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

The unexpected results that higher income and more expensive cigarettes were associated with lower odds of abstinence, whereas regional smoking prevalence was not significantly associated with short-term cessation, provide insight to a more nuanced interpretation of the "hardening hypothesis," which could prove valuable in tackling the end stages of the tobacco epidemic.

INTRODUCTION

An estimated 1.3 billion (roughly 1 in 5) people worldwide use tobacco [1]. Although global smoking prevalence is decreasing [2], the number of smokers continues to increase [2]. Smoking is the leading cause of preventable death worldwide [3]. Tobacco-related deaths are increasing [2], with more than 8 million deaths per year attributable to tobacco [1].

As of 2017, high-income countries still had higher smoking prevalence rates (21.6%) than low- (11.2%) and middle-income (19.5%) countries [4]. However, high-income countries also show disproportionately greater reductions in smoking prevalence than low- and middle-income countries [5]. As a result, low- to middle-income countries are now home to 80% of the world's population of smokers [1] and report the majority of tobacco-related deaths [6].

Smoking prevalence also varies greatly by geographic region. According to the World Health Organization (WHO) prevalence estimates for 2015, the European region had the highest smoking rates (29.9%), followed by the Western Pacific region (24.8%); the African region had the lowest (10.0%) [4]. Although smoking prevalence is decreasing (and expected to continue decreasing) in most regions, the eastern Mediterranean is projected to be an exception [6].

In 2003, to address these disparities, WHO established the Framework Convention on Tobacco Control (FCTC), which outlines policies and measures to promote tobacco use prevention and treatment globally [7]. To track the progress of individual countries, WHO developed a quantitative measure – the MPOWER score. This grades a country's tobacco control efforts across six domains (Table 1). Countries with higher MPOWER scores showed greater reduction in smoking prevalence over the first decade of FCTC implementation [8]. However, regional disparities in overall tobacco use prevalence cannot be fully addressed without understanding the contributors to such disparities, specifically whether these could also be

influencing regional cessation rates. Individual-level predictors of smoking cessation are widely studied in the literature. Fewer studies have explored how country of origin might influence abstinence. The International Tobacco Control Four Country Survey (ITC-4) was a large prospective cohort study that involved telephone surveys of more than 2000 smokers in Australia, Canada, the United Kingdom, and the United States. An analysis of the ITC-4 data by Hyland *et al* [9] demonstrated that these countries' smoking cessation rates were not equally moderated by traditional individual predictors such as the Heaviness of Smoking Index, and favorable attitudes about smoking and self-efficacy for quitting. Furthermore, heaviness of smoking was associated with lower income in all countries but the United States [10].

Table 1 Country-level economic, epidemiologic, and policy variables

Tobacco prevalence	Tobacco smoking prevalence in 2015 [5]
GDP *per capita*	GDP *per capita* in US dollars in 2014 [11]
Cigarette relative income price	Relative cost of cigarettes calculated as percentage of GDP *per capita* required to purchase 2000 cigarettes of the most sold brand in 2014 [5]
MPOWER score	A quantitative measure of tobacco control policy developed by the World Health Organization to support policy implementation under the Framework Convention on Tobacco Control [12]. It is based on a composite score (out of a total of 37) of six core measures: **M** = Monitoring tobacco use and prevention policies **P** = Protecting people from tobacco smoke **O** = Offering help to quit tobacco use **W** = Warning about the dangers of tobacco **E** = Enforcing bans on tobacco advertising, promotion and sponsorship **R** = Raising taxes on tobacco

GDP, gross domestic product.

Our prior work similarly noted regional effects on smoking cessation rates, while also incorporating the impact of pharmacotherapy. One secondary analysis of a study examining the effect of varenicline on depressed smokers demonstrated that European participants were four times more likely to achieve abstinence than US participants, and that higher levels of baseline depressive symptoms were associated with lower abstinence rates for European but not US participants [13].

One proposed explanation for these results is the "hardening hypothesis" – that areas with lower smoking prevalence are composed of more "hardened" smokers who have greater difficulty quitting. Smokers who found it easier to quit have already quit, and the remaining hardened smokers are more nicotine dependent, of lower socioeconomic status, and have greater likelihood of psychiatric comorbidity [14]. This hypothesis has been difficult to consistently support [14-16]. A major gap within the "hardening" literature is that most studies have been conducted in high-income countries [14]. If hardening were to be demonstrated on a broader global scale, there could be significant implications for international tobacco policy.

Similar limitations exist in the literature on predictors of smoking cessation: regional differences are primarily examined among high-income, Westernized countries. Fewer studies include geographically and economically diverse countries. Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) was a large-scale, multinational, randomized, placebo-controlled, smoking cessation pharmacotherapy study, conducted from 2011 to 2015, that offered a unique opportunity to examine smoking cessation outcomes on a global level [17]. Participants were recruited from 16 high- and middle-income countries across five continents. There were significant regional differences in smoking cessation outcomes [18], with lower abstinence rates in, compared with outside, the United States (even after controlling for other factors).

This paper explores these findings from EAGLES, as, to our knowledge, no large-scale randomized controlled trials have examined global regional differences in predictors of smoking cessation outcomes among both high- and middle-income countries. Our first aim was to examine regional demographic, smoking, and psychiatric differences, and we hypothesized that significant baseline differences would be observed across regions. Our second aim was to

explore whether region- and country-specific variables – such as income, cigarette affordability, prevalence of tobacco use, and tobacco control policy – were associated with cessation outcomes. We hypothesized that participants from countries with more proactive tobacco control policies would have a less robust response to smoking cessation interventions than their counterparts due to possible "hardening."

METHODS

Design

This is a secondary analysis of data collected from EAGLES (CinicalTrials.gov NCT01456936), which investigated the safety and efficacy of varenicline (1 mg twice daily) and bupropion (150 mg twice daily) in a randomized active- (nicotine patch, 21 mg/day) and placebo-controlled trial in 8144 smokers with (n=4116) and without (n=4028) psychiatric disorders. Participants received 12 weeks of active treatment (or placebo) and were followed for an additional 12 weeks, and all participants received brief cessation counseling. The primary outcome paper includes further details about study methodology and follows reporting recommendations set out by CONSORT guidelines [17, 19]

Participants

Participants were male and female smokers, aged 18–75 years, who were motivated to quit smoking and smoked, on average, ≥10 cigarettes per day. Those in the psychiatric cohort (PC) met DSM-IV-TR [20] criteria for either a mood disorder (major depressive or bipolar disorders), anxiety disorder (panic, post-traumatic stress or obsessive compulsive disorder, social phobia or generalized anxiety disorder), psychotic disorder (schizophrenia or schizoaffective disorder), or borderline personality disorder as confirmed by the Structured Clinical Interview for the DSM-

IV-TR for Axis I/II disorders (SCID-I/II) [21, 22]. Participants in the non-psychiatric cohort (NPC) had no history of mental illness, as confirmed by SCID-I/II. For this secondary analysis, we grouped countries into seven regions based on their geographic proximity and similarities in demographic characteristics (Table 2).

Table 2 Country-specific variables by region

Region	Country	Tobacco prevalence*	GDP *per capita*†	Cigarette relative income price‡	MPOWER score§
North America	United States	21.5	55 048	1.1	22
	Canada	14.4	50 893	1.7	32
Central America	Mexico	14.7	10 922	3.1	26
South America	Argentina	22.0	12 335	1.4	33
	Brazil	14.4	12 113	2	34
	Chile	37.5	14 671	2	28
Eastern Europe	Bulgaria	33.4	7874	4.1	29
	Russian Federation	37.6	18 671	2	26
	Slovakia	28.9	14 096	1.2	30
Western Europe	Denmark	20.0	62 549	1.3	27
	Finland	18.7	50 260	1.5	29
	Germany	27.0	47 960	1.5	23
	Spain	26.0	29 462	2.2	30
Africa	South Africa	20.1	6433	4.5	14
Australasia	Australia	14.6	62 511	2.5	32
	New Zealand	15.3	44 553	3.2	28

* Tobacco smoking prevalence in 2015 [5].

† GDP *per capita* in 2014 (*per capita* in USD) [11].

‡ Relative cost of cigarettes as a percentage of GDP *per capita* required to purchase 2000 cigarettes of the most sold brand [1].

§ MPOWER policy score in 2015 (out of 37) [2].

GDP, gross domestic product; USD, United States dollars.

Primary outcome measure

The primary outcome for this secondary analysis was 7-day point prevalence abstinence (PPA) at the end of treatment (week 12), selected to amplify the abstinence signal as early abstinence has

been shown to strongly predict future long-term abstinence [23]. Abstinence was verified biochemically with exhaled carbon monoxide levels <10 parts per million.

EAGLES independent variables

Participant characteristics associated with continuous abstinence from 9 to 24 weeks were included as candidate predictor terms in this secondary analysis [18]. These included age, gender, body mass index (BMI), race (White vs non-White), nicotine dependence severity (measured by Fagerström Test for Cigarette Dependence [FTCD]) [24], cigarettes per day in the month prior to enrollment, prior use of smoking cessation medications (varenicline, bupropion, or nicotine replacement therapy [NRT]), age when started smoking, lives with smoker and has contact with smokers. Additionally, we included seven mental health characteristics: comorbid psychiatric diagnosis (none, mood disorder, anxiety disorder, psychotic disorder) [20]; depression symptom severity (measured by Hospital Anxiety and Depression Scale [HADS]) [25]; anxiety symptom severity (measured by HADS) [25]; aggression symptom severity (measured by Buss–Perry Aggression Questionnaire) [26]; lifetime suicidal behavior and/or ideation (yes/no, measured by Columbia–Suicide Severity Rating Scale) [27]; comorbid alcohol or other substance dependence (defined by DSM-IV-TR and confirmed by SCID-I/II) [20]; and use of psychotropic medication (yes/no).

Non-EAGLES country-level independent variables

Four country-specific variables were sourced to reflect their values during the period in which EAGLES was conducted (2011–2015) (Table 1).

Baseline tobacco smoking prevalence was extracted from WHO statistics on smoking prevalence rates from 2015 [5]. To measure the regional economic influence on cessation

outcomes, both absolute and relative measures were obtained. The gross domestic product (GDP) of each country was measured as GDP *per capita* in US dollars in 2014 (as reported by the World Bank) [11], which was then divided by 10 000 to facilitate effect interpretation. To look at the affordability of cigarettes in a country, we use the "relative income price" (RIP) measure, calculated as the percentage of GDP *per capita* required to purchase 2000 cigarettes (100 packs) of the most sold brand (data from 2014 [5]).

The rigor of each country's tobacco control policy was estimated using the WHO's 37-point MPOWER score, which quantifies the degree of implementation and enforcement of the FCTC. Points are awarded according to six core domains (Table 1) [12]. A higher score indicates greater adherence to FCTC guidelines, with a maximum possible score of 37. Table 2 illustrates the country-level variables (tobacco prevalence, GDP, cigarette RIP, and MPOWER score) we derived for all 16 countries in which EAGLES participants were enrolled. It further depicts the seven geographic regions we characterized to capture these regional differences. Each EAGLES participant was assigned values for these four variables corresponding to the location of their respective study site.

Statistical analysis

Descriptive statistics were compiled to examine baseline differences by country and geographic region, with respect to demographic, smoking, and mental health characteristics. A correlation assessment for the country-level variables was reviewed to alleviate any multicollinearity concerns with these measures. For the primary efficacy endpoint of 7-day PPA at week 12, model building used a stepwise, logistic regression analysis. Significance levels were set *a priori* as 10% for a variable to enter and 15% to remain in the model. The method forced inclusion of treatment condition (placebo, varenicline, bupropion, NRT) and cohort (PC and NPC). Main-

effect candidates included regions (7-level), four country-level non-EAGLES variables, and 17 EAGLES baseline characteristics, described above. All randomized subjects were included, with odds ratios [ORs] (95% confidence intervals [CIs]) computed.

RESULTS

Smoking prevalence rates varied widely across the countries and regions represented in EAGLES (Table 3). Smoking rates were highest in the Russian Federation and Eastern Europe. Australia, Brazil, Canada, and Mexico had smoking prevalence rates below 15%. There was also marked variability in countries' GDP, with Denmark and Australia registering as the highest income countries, and South Africa and Bulgaria as the lowest among EAGLES countries. Relative cost of cigarettes was highest in South Africa and Bulgaria; the United States had the lowest cigarette RIP in 2014. MPOWER scores ranged from a low of 14 in South Africa to a high of 34 in Brazil. These four variables were not significantly correlated (data not shown).

Mean tobacco smoking prevalence was highest in Eastern Europe (32.8%) and tied for lowest in Australasia and Central America (15.0%). Although Central America (Mexico) had the lowest proportion of participants with psychiatric diagnosis and no active substance use disorders, participants enrolled in this country had the highest baseline levels of anxiety (5.8 ± 4.1), depression (3.7 ± 3.2), and aggression (62.2± 17.8) scores. South Africa had the lowest GDP *per capita* (6433 ± 0.0) and lowest MPOWER policy score (14.0 ± 0.0). South America had the highest MPOWER score (32.8 ± 1.1).

Table 3 Baseline characteristics by region (demographic, smoking, psychiatric, and country-level variables)

Category	Variable		All (N=8144)	North America (n=4539)	Central America (n=188)	South America (n=371)	Eastern Europe (n=818)	Western Europe (n=1750)	Africa (n=296)	Australasia (n=182)
Demographic characteristics	Age, years, mean (SD)		46.5 (12.3)	46.5 (12.4)	47.6 (11.7)	51.7 (11.2)	42.9 (11.8)	48.1 (11.4)	42.1 (13.7)	43.2 (13.8)
	Race	White	6649 (81.6)	3304 (72.8)	184 (97.9)	368 (99.2)	818 (100)	1736 (99.2)	116 (39.2)	123 (67.6)
		Black	1162 (14.2)	1071 (23.6)	1 (0.5)	2 (0.5)	0 (0)	2 (0.1)	86 (29.1)	0 (0)
		Other	332 (4.1)	163 (3.6)	3 (1.6)	1 (0.3)	0 (0)	12 (0.7)	94 (31.8)	59 (32.4)
	Gender	Male	3592 (44.1)	1907 (42.0)	93 (49.5)	169 (45.6)	394 (48.2)	790 (45.1)	166 (56.1)	73 (40.1)
		Female	4552 (55.9)	2632 (58.0)	95 (50.5)	202 (54.4)	424 (51.8)	960 (54.9)	130 (43.9)	109 (59.9)
Smoking characteristics	FTCD score, mean (SD)		5.8 (2.0)	5.7 (1.9)	5.5 (2.1)	5.5 (2.3)	6.2 (2.1)	5.8 (2.0)	5.9 (1.9)	5.5 (2.0)
	Cigarettes per day in past month, mean (SD)		20.7 (8.2)	19.5 (7.7)	19.5 (7.7)	26.6 (11.4)	23.1 (8.1)	21.7 (7.9)	19.7 (9.2)	18.9 (7.0)
	Living with smoker		2931 (36.0)	1655 (36.5)	69 (36.7)	134 (36.1)	398 (48.7)	486 (27.8)	125 (42.2)	64 (35.2)
	Prior treatment	Prior varenicline use	1271 (15.6)	934 (20.6)	7 (3.7)	10 (2.7)	1 (0.1)	236 (13.5)	18 (6.1)	65 (35.7)
		Prior bupropion use	844 (10.4)	640 (14.1)	1 (0.5)	17 (4.6)	0 (0)	127 (7.3)	39 (13.2)	20 (11.0)
		Prior NRT use	2136 (26.2)	1551 (34.2)	9 (4.8)	3 (0.8)	27 (3.3)	450 (25.7)	20 (6.8)	76 (41.8)
Psychiatric characteristics	Comorbid psychiatric diagnosis		1511 (18.6)	1092 (24.1)	2 (1.1)	42 (11.3)	13 (1.6)	282 (16.1)	31 (10.5)	49 (26.9)
	No primary mood disorder		4028 (49.5)	2037 (44.9)	134 (71.3)	243 (65.5)	446 (54.5)	843 (48.2)	225 (76.0)	100 (54.9)
	Primary mood disorder		2910 (35.7)	1883 (41.5)	44 (23.4)	50 (13.5)	138 (16.9)	691 (39.5)	56 (18.9)	48 (26.4)
	Primary anxiety disorder		792 (9.7)	424 (9.3)	6 (3.2)	69 (18.6)	110 (13.4)	156 (8.9)	4 (1.4)	23 (12.6)

Category	Variable	All (N=8144)	North America (n=4539)	Central America (n=188)	South America (n=371)	Eastern Europe (n=818)	Western Europe (n=1760)	Africa (n=296)	Australasia (n=182)
	Primary psychotic disorder	390 (4.8)	193 (4.3)	2 (1.1)	4 (1.1)	121 (14.8)	49 (2.8)	10 (3.4)	11 (6.0)
	Borderline personality disorder	24 (0.3)	2 (<0.1)	2 (1.1)	5 (1.3)	3 (0.4)	11 (0.6)	1 (0.3)	0 (0)
	HADS anxiety score, mean (SD)	4.0 (3.6)	4.2 (3.6)	5.8 (4.1)	3.4 (2.9)	2.2 (2.7)	4.2 (3.9)	3.8 (3.7)	4.6 (3.5)
	HADS depression score, mean (SD)	2.4 (2.9)	2.4 (2.9)	3.7 (3.2)	2.1 (2.5)	2.0 (2.6)	2.4 (3.1)	2.2 (2.5)	2.3 (2.8)
	Aggression Q total score, mean (SD)	55.5 (17.4)	54.5 (18.2)	62.2 (17.8)	62.2 (17.1)	55.2 (15.7)	55.5 (17.2)	58.6 (17.2)	56.6 (17.0)
	C-SSRS BEID	1623 (19.9)	1010 (22.3)	37 (19.7)	25 (6.7)	14 (1.7)	430 (24.4)	40 (13.5)	67 (36.8)
	Alcohol/substance dependence/use	957 (11.8)	778 (17.1)	0 (0)	12 (3.2)	5 (0.6)	109 (6.2)	17 (5.7)	36 (19.8)
	Any psychotropic medication use	2325 (28.5)	1459 (32.1)	22 (11.7)	80 (21.6)	294 (35.9)	377 (21.5)	51 (17.2)	42 (23.1)
Newly derived country-specific variables	Tobacco prevalence, mean (SD)	22.9 (4.6)	21.5 (1.9)	15.0 (0.0)	22.3 (3.9)	32.8 (2.8)	24.1 (7.7)	20.0 (0.0)	15.0 (0.0)
	GDP, mean (SD)	43 972.4 (17 700.4)	54 792.6 (998.1)	10 922.0 (0.0)	12 429.5 (494.5)	11 498.7 (4651.8)	47 028.9 (7833.6)	6433.0 (0.0)	50 177.2 (8351.7)
	Cigarette RIP, mean (SD)	1.7 (1.0)	1.1 (0.1)	3.1 (0.0)	1.5 (0.2)	3.1 (1.2)	1.6 (0.3)	4.5 (0.0)	3.0 (0.3)
	MPOWER score, mean (SD)	24.3 (4.2)	22.6 (2.4)	26.0 (0.0)	32.8 (1.1)	28.4 (1.4)	25.9 (2.1)	14.0 (0.0)	29.3 (1.9)

All data are given as n (%) unless otherwise specified.

BEID, behavior and/or ideation; C-SSRS, Columbia–Suicide Severity Rating Scale; FTCD, Framework Convention on Tobacco Control; GDP, gross domestic product; HADS, Hospital Anxiety and Depression Scale; NRT, nicotine replacement therapy; Q, questionnaire; RIP, relative income price; SD, standard deviation.

Seven-day end-of-treatment PPA varied widely across regions (Figure 1), with the lowest rates found in Australasia (22.0%) and North America (22.5%) and the highest rate (55.9%) in Central America.

Table 4 depicts the results of the stepwise regression model examining the association of the 17 candidate predictor variables and the primary endpoint of 7-day PPA. Consistent with prior analyses of EAGLES data, individuals of Black compared to White race (OR 0.622 [95% CI 0.518, 0.748]), with psychotic disorders (0.605 [0.435, 0.841]), psychiatric medication use (0.789 [0.688, 0.904]), more cigarettes per day (0.968 [0.960, 0.976]) and contact with a smoker (0.856 [0.764, 0.961]) had lower odds of achieving short-term abstinence. Higher abstinence rates were observed in older participants (OR 1.010 [95% CI 1.005, 1.014]), with greater BMI (1.013 [1.004, 1.022]) and with prior varenicline use (1.228 [1.060, 1.422]). Additionally, all treatment groups demonstrated higher odds of abstinence as compared to placebo, as follows: varenicline (OR 3.808 [95% CI 3.260, 4.447]), bupropion (2.059 [1.755, 2.417]) and NRT (2.103 [1.793, 2.468]).

Table 4 Main-effect odds ratios for final stepwise logistic regression model of 7-day PPA, week 12

Effect*		Odds ratio estimate	95% lower CI	95% upper CI
Demographics	Age	1.010	1.005	1.014
	BMI	1.013	1.004	1.022
	Black race (vs White)	0.622	0.518	0.748
Psychiatric characteristics	Psychotic disorder	0.605	0.435	0.841
	Use of psychiatric medications	0.789	0.688	0.904
Smoking characteristics	FTND	0.907	0.879	0.936
	Cigarettes per day	0.968	0.960	0.976
	Contact with smoker	0.856	0.764	0.961
	Prior varenicline	1.228	1.060	1.422
Treatment group (vs placebo)	Varenicline	3.808	3.260	4.447
	Bupropion	2.059	1.755	2.417

	NRT	2.103	1.793	2.468
Region (vs North America)	Eastern Europe	0.390	0.222	0.686
	South America	0.170	0.083	0.348
	Western Europe	1.356	1.140	1.613
Country-level variables	GDP†	0.544	0.468	0.631
	Cigarette RIP	0.617	0.528	0.722
	MPOWER	1.031	1.008	1.055

BMI, body mass index; CL, confidence interval; FTND, Fagerström Test for Nicotine Dependence; GDP, gross domestic product; NRT, nicotine replacement therapy; PPA, point prevalence abstinence; RIP, relative income price.

* Only most significant effects shown.

† GDP *per capita* per $10,000 USD.

After controlling for those traditional predictor variables, region remained in the model as a significant main effect. Using North America (United States and Canada) as the referent, odds of achieving short-term abstinence were significantly higher in the Western European (OR 1.356 [95% CI 1.140, 1.613]) and lower in the Eastern European (0.390 [0.222, 0.686]) and South American (0.170 [0.083, 0.348]) regions.

Of the four country-level variables, three predicted abstinence (Table 4). Lower odds of abstinence were seen with higher GDP (OR 0.544 [95% CI 0.468, 0.631]) and higher cigarette RIP (0.617 [0.528, 0.722]), whereas higher odds were seen with higher MPOWER score (1.031 [1.008, 1.055]). Notably, tobacco smoking prevalence was not included in the model.

DISCUSSION

As predicted, individual-level variables of demographic, psychiatric, and smoking-related characteristics, as well as country-level variables of income, cigarette relative income price, and implementation of tobacco control policy, were associated with the likelihood of quitting. Specifically, the higher the income of a country and the more expensive cigarettes, the lower the likelihood of abstinence at end of treatment. Conversely, more stringent tobacco control policy

implementation was associated with increased rates of abstinence. Finally, country-level tobacco prevalence at the time the EAGLES study was conducted was not significantly correlated with abstinence initiation rates. After controlling for these and other traditional predictor variables, global region was still found to be a significant independent predictor of short-term smoking abstinence.

Despite adhering to the same study protocol, baseline characteristics by region differed broadly across the board with respect to age, gender, race, psychiatric history, psychiatric symptoms, prior treatments, severity of tobacco use and dependence, and substance use history. For instance, participants enrolled in the South American region were the oldest, smoked the most cigarettes per day, and were 99% White; Africa was the only region where males predominated and participants were predominantly non-White. Some regions had a substantial number of participants who had previously tried smoking cessation treatments, but regions such as Eastern Europe and Central America had hardly any. These individual-level characteristics have been shown to be independently associated with tobacco cessation outcomes, both in our earlier analysis [18] and in the literature more generally [13, 23, 28]. There is a growing body of literature suggesting the benefit of interventions specific to these risk factors [29-31], and one might extrapolate a potential benefit in tailoring a region's tobacco control plan to its unique characteristic makeup.

We found that a greater degree of tobacco control policy implementation, as reflected by higher MPOWER scores, was associated with higher odds of achieving short-term abstinence in EAGLES. This suggests that greater tobacco regulation is associated with higher quit rates, which is corroborated by the literature [32] and aligns with the greater mission of the FCTC. Although it may be presumed that greater tobacco control would be found in higher-income

regions and reflected by higher-priced and taxed cigarettes, our analysis did not find that to be the case. In fact, not only did we *not* find a correlation between those variables, but we found an inverse relationship with cessation rates. Our analysis found that higher income and more expensive cigarettes (i.e., higher RIP) were associated with lower cessation rates. This comes as a surprise among the growing body of literature reporting that higher-income countries have had more drastic reductions in smoking prevalence [5], thought to be due to greater funding for and access to cessation interventions [33]. However, a newer, large-scale global analysis, published by Sathish *et al* [34], found that smokers in high-income countries were consuming cigarettes with much higher levels of nicotine than those in middle- or lower-income countries, which might make it harder to quit [34]. The literature also supports the idea that increasing the price of cigarettes is associated with a greater likelihood of quitting [6, 35], which is in opposition to our finding.

One possible explanation for these curious results is the controversial "hardening hypothesis" that smokers who find it easier to quit have already done so, leaving "hardened" smokers. If someone continues to smoke cigarettes despite the increasing cost, that individual may fall under the umbrella of a "hardened" smoker, and thus have more difficulty quitting. The same may apply to higher-income regions, with presumed greater access to healthcare and cessation resources. However, hardening is commonly attributed to populations with lower smoking prevalence [14-16], and in our analysis, a region's smoking prevalence rate at the time EAGLES was conducted was not a significant predictor of smoking cessation success once other variables were included in the model. Basing the hardening hypothesis purely on smoking prevalence at a single time point is likely too reductionist a model. For example, Cheung *et al* found a model that may unite contradictory findings about hardening [36]. Their sample showed

a U-shaped relationship between the odds of quitting smoking and smoking prevalence, in which odds of quitting were highest at either extreme of the smoking prevalence curve.

Even though we examined these regional effects in a more granular, seven-region context compared with our prior EAGLES analyses, which considered only a US/non-US dichotomy, the region from which subjects were enrolled remained a significant main effect in the analytic model despite also controlling for treatment group and psychiatric subcohort. The EAGLES dataset was not intended to represent the global population of smokers at large, nor was its enrollment strategy designed to randomize participants within each of the countries participating. Nevertheless, our regional findings appeared to have similar trends to others described in the literature. Our prior work [13] did not make the distinction between Eastern and Western Europe, but found that European smokers had higher rates of abstinence overall compared with US smokers. In our current analysis, we found that, when compared to North American participants, smokers enrolled in the Western European region had approximately one-third higher odds of abstinence, whereas enrollees in Eastern Europe had less than half the odds of quitting. The literature supports this finding, and when compared to Western Europe, Eastern Europe has been found to have lower smoking cessation rates [37], higher smoking prevalence rates, and higher rates of morbidity and mortality attributable to tobacco [5]. These challenges are thought to be due to more accessible cigarettes, less tobacco control, and particular cultural and religious practices in the region [5]. We also found that smokers enrolled at sites in South America had the lowest odds of successful cessation – about one-quarter of the odds in North America (Table 4). A 2008 review paper from Muller and Wehbe [38] examined unique factors in Latin America that contribute to its growing tobacco epidemic, particularly that this region includes some of the highest tobacco-producing countries in the world (in our dataset, Brazil #3 and Argentina #9),

and that such an economic reliance on tobacco products has likely contributed to less rigorous tobacco control, less expensive cigarettes, and an ongoing tobacco smuggling trade [38]. It is curious then, in our analysis, that this region had the *highest* MPOWER score. Because our model was designed to include all regions, each predictor might not extrapolate to each individual region.

Our analyses were not without limitations. The EAGLES trial was not designed to recruit representative samples of a country's smokers, but rather, to enroll smokers who met prespecified inclusion/exclusion criteria into a methodologically sound, randomized controlled trial comparing the first-line smoking cessation medications and placebo. Thus, the results might not generalize to the global population of smokers at large and may not be representative of each country's smokers. Sites enrolling participants in EAGLES were located primarily in high- and upper-middle income countries, further limiting generalizability. Over half the EAGLES participants were enrolled in the United States, an imbalance that could have affected results. Although we controlled for treatment condition and psychiatric cohort in our analyses and examined correlations among the newly introduced country-level variables, we cannot rule out multicollinearity among predictor variables affecting the results. Nonetheless, EAGLES remains the largest, most rigorous, placebo-controlled, multinational trial of smoking cessation medications ever conducted, and the new results obtained will help inform subsequent analyses in samples more representative of smokers across the globe.

In conclusion, geographic region had a significant effect on the odds of achieving short-term smoking abstinence in EAGLES even after controlling for treatment, psychiatric comorbidity, individual-level, and country-specific variables. Increased tobacco control policy and enforcement was associated with greater chance of achieving short-term abstinence, which

supports the argument that tighter regulation is associated with enhanced efficacy of smoking cessation treatments. Although seemingly contradictory, increased income of a country and more expensive cigarettes were associated with lower odds of abstinence, which might reflect hardening of smokers in those countries. The literature remains mixed about whether hardening truly exists; it may be that a deeper understanding of this complex phenomenon is needed, rather than refuting the validity of the hypothesis itself.

<END MATTER>

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Contributors All authors were involved in the analyses and/or interpretation of the data. DEL performed the statistical analyses. All authors were involved in the drafting of the manuscript and revising it critically for intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Patient consent for publication All patients provided written, informed consent and were reimbursed for study participation time and travel expenses as determined by each trial site.

Ethics approval EAGLES was reviewed and approved by each site's institutional review board or ethics committee and was conducted in accordance with the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines.

Data availability statement Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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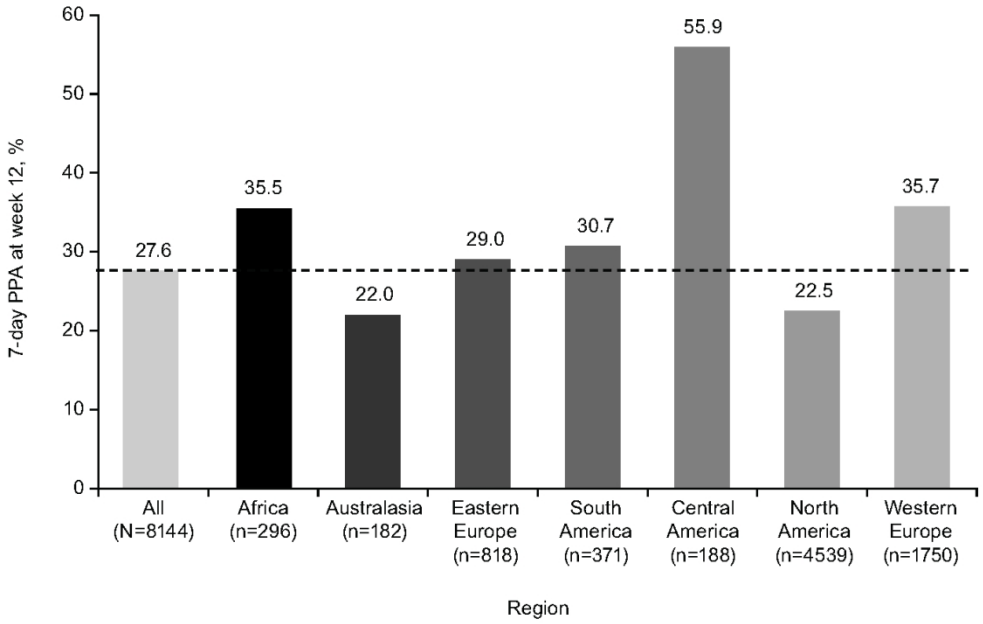
<FIGURE LEGEND>

Figure 1 Seven-day PPA at week 12 by region. All patients randomized. PPA, point prevalence abstinence.



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		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	3
Introduction			

Background and objectives	#2a	Scientific background and explanation of rationale	5-6
Background and objectives	#2b	Specific objectives or hypothesis	7-8
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	8*
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	8*
Participants	#4a	Eligibility criteria for participants	8-9
Participants	#4b	Settings and locations where the data were collected	7-8*
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8*
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	9-10
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	8*
Sample size	#7a	How sample size was determined.	8*

Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	8*
			8*
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size) - 8*	
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8*
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	8*
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	8*
Blinding	#11b	If relevant, description of the similarity of interventions	8*
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	11-12

Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11-12
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8*
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	8*
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	8*
Recruitment	#14b	Why the trial ended or was stopped	8*
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	14-15
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8*
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16-17
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	15-16

Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8*
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	8*
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	21
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-20
Registration	#23	Registration number and name of trial registry	8
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-20
Registration	#23	Registration number and name of trial registry	8
Protocol	#24	Where the full trial protocol can be accessed, if available	8*
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	23

*Referenced in the paper but more explicitly elaborated in primary outcome paper (Anthenelli RM, Benowitz NL, West R, *et al.* Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387:2507-20)

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Economic and tobacco regulatory factors influence smoking cessation outcomes in the multinational EAGLES randomized controlled trial

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Economic and tobacco regulatory factors influence smoking cessation outcomes in the multinational EAGLES randomized controlled trial

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ABSTRACT

Introduction We previously reported global regional differences in smoking cessation outcomes, with smokers of United States origin having lower quit rates than smokers from some other countries. This post hoc analysis examined global regional differences in individual- and country-level epidemiologic, economic, and tobacco regulatory factors that may affect cessation outcomes.

Methods EAGLES (NCT01456936) was a randomized controlled trial that evaluated first-line cessation medications and placebo in 8144 smokers with and without psychiatric disorders from 16 countries across seven regions. Generalized linear and stepwise logistic regression models that considered pharmacotherapy treatment, psychiatric diagnoses, traditional individual-level predictors (e.g., demographic and smoking characteristics), and country-specific smoking prevalence rates, gross domestic product (GDP) per capita, relative cigarette cost, and WHO-derived MPOWER scores were used to predict 7-day point prevalence abstinence at the end of treatment.

Results In addition to several traditional predictors, three of four country-level variables predicted short-term abstinence: GDP (0.54 [95% CI 0.47, 0.63]), cigarette relative income price (0.62 [0.53, 0.72]), and MPOWER score (1.03 [1.01, 1.06]). Quit rates varied across regions (22.0% in Australasia to 55.9% in Mexico). With northern North America (United States and Canada) as the referent, the likelihood of achieving short-term abstinence was significantly higher in Western Europe (OR 1.4 [95% CI 1.14, 1.61]), but significantly lower in Eastern Europe (0.39 [0.22, 0.69]) and South America (0.17 [0.08, 0.35]).

Conclusions Increased tobacco regulation was associated with enhanced quitting among participants in the EAGLES trial. Paradoxically, lower GDP, and more affordable cigarette

pricing relative to a country's GDP, were also associated with higher odds of quitting. Geographic region was also a significant independent predictor.

Strengths and limitations of this study

- EAGLES is the largest randomized, placebo-controlled trial of cessation medications that enrolled persons with and without psychiatric disorders who smoke in 16 high- and middle-income countries across five continents
- The present *post-hoc* analysis of EAGLES trial results extends prior work by incorporating novel country- and region-specific factors as predictors of smoking cessation outcomes
- The EAGLES trial was not designed to recruit representative samples of a country's smokers; but rather, to enroll smokers who met prespecified inclusion/exclusion criteria, which may limit generalizability

WHAT THIS STUDY ADDS

WHAT IS ALREADY KNOWN ON THIS TOPIC

Population-based studies examining individual and country-level factors associated with abstinence after a quit attempt have found wide variation across countries and inconsistent support of the "hardening hypothesis," which posits that smokers in countries with low smoking prevalence will possess characteristics that make it harder to quit. However, those studies focused on high-income countries like the United States and Canada, the European Union, and Australia and did not examine a standardized response to the first-line smoking cessation medications.

WHAT THIS STUDY ADDS

EAGLES is the largest, randomized, placebo-controlled trial of cessation medications ever conducted that enrolled smokers with and without psychiatric disorders in 16 high- and middle-income countries across five continents. The authors found that in addition to several traditional individual-level factors predicting short-term cessation success, increased tobacco regulation, lower relative cigarette cost, and lower GDP were associated with enhanced quitting.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

The unexpected results that higher income and more expensive cigarettes were associated with lower odds of abstinence, whereas regional smoking prevalence was not significantly associated with short-term cessation, provide insight to a more nuanced interpretation of the "hardening hypothesis," which could prove valuable in tackling the end stages of the tobacco epidemic.

INTRODUCTION

An estimated 1.3 billion (roughly 1 in 5) people worldwide use tobacco [1]. Although global smoking prevalence is decreasing [2], the number of smokers continues to increase [2]. Smoking is the leading cause of preventable death worldwide [3]. Tobacco-related deaths are increasing [2], with more than 8 million deaths per year attributable to tobacco [1].

As of 2017, high-income countries still had higher smoking prevalence rates (21.6%) than low- (11.2%) and middle-income (19.5%) countries [4]. However, high-income countries also show disproportionately greater reductions in smoking prevalence than low- and middle-income countries [5]. As a result, low- to middle-income countries are now home to 80% of the world's population of smokers [1] and report the majority of tobacco-related deaths [6].

Smoking prevalence also varies greatly by geographic region. According to the World Health Organization (WHO) prevalence estimates for 2015, the European region had the highest smoking rates (29.9%), followed by the Western Pacific region (24.8%); the African region had the lowest (10.0%) [4]. Although smoking prevalence is decreasing (and expected to continue decreasing) in most regions, the eastern Mediterranean is projected to be an exception [6].

In 2003, to address these disparities, WHO established the Framework Convention on Tobacco Control (FCTC), which outlines policies and measures to promote tobacco use prevention and treatment globally [7]. To track the progress of individual countries, WHO developed a quantitative measure – the MPOWER score. This grades a country's tobacco control efforts across six domains (Table 1). Countries with higher MPOWER scores showed greater reduction in smoking prevalence over the first decade of FCTC implementation [8]. However, regional disparities in overall tobacco use prevalence cannot be fully addressed without understanding the contributors to such disparities, specifically whether these could also be

influencing regional cessation rates. Individual-level predictors of smoking cessation are widely studied in the literature. Fewer studies have explored how country of origin might influence abstinence. The International Tobacco Control Four Country Survey (ITC-4) was a large prospective cohort study that involved telephone surveys of more than 2000 smokers in Australia, Canada, the United Kingdom, and the United States. An analysis of the ITC-4 data by Hyland *et al* [9] demonstrated that these countries' smoking cessation rates were not equally moderated by traditional individual predictors such as the Heaviness of Smoking Index, and favorable attitudes about smoking and self-efficacy for quitting. Furthermore, heaviness of smoking was associated with lower income in all countries but the United States [10].

Table 1 Country-level economic, epidemiologic, and policy variables

Tobacco prevalence	Tobacco smoking prevalence in 2015 [5]
GDP *per capita*	GDP *per capita* in US dollars in 2014 [11]
Cigarette relative income price	Relative cost of cigarettes calculated as percentage of GDP *per capita* required to purchase 2000 cigarettes of the most sold brand in 2014 [5]
MPOWER score	A quantitative measure of tobacco control policy developed by the World Health Organization to support policy implementation under the Framework Convention on Tobacco Control [12]. It is based on a composite score (out of a total of 37) of six core measures: **M** = Monitoring tobacco use and prevention policies **P** = Protecting people from tobacco smoke **O** = Offering help to quit tobacco use **W** = Warning about the dangers of tobacco **E** = Enforcing bans on tobacco advertising, promotion and sponsorship **R** = Raising taxes on tobacco

GDP, gross domestic product.

Our prior work similarly noted regional effects on smoking cessation rates, while also incorporating the impact of pharmacotherapy. One secondary analysis of a study examining the effect of varenicline on depressed smokers demonstrated that European participants were four times more likely to achieve abstinence than US participants, and that higher levels of baseline depressive symptoms were associated with lower abstinence rates for European but not US participants [13].

One proposed explanation for these results is the "hardening hypothesis" – that areas with lower smoking prevalence are composed of more "hardened" smokers who have greater difficulty quitting. Smokers who found it easier to quit have already quit, and the remaining hardened smokers are more nicotine dependent, of lower socioeconomic status, and have greater likelihood of psychiatric comorbidity [14]. This hypothesis has been difficult to consistently support [14-16]. A major gap within the "hardening" literature is that most studies have been conducted in high-income countries [14]. If hardening were to be demonstrated on a broader global scale, there could be significant implications for international tobacco policy.

Similar limitations exist in the literature on predictors of smoking cessation: regional differences are primarily examined among high-income, Westernized countries. Fewer studies include geographically and economically diverse countries. Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) was a large-scale, multinational, randomized, placebo-controlled, smoking cessation pharmacotherapy study, conducted from 2011 to 2015, that offered a unique opportunity to examine smoking cessation outcomes on a global level [17]. Participants were recruited from 16 high- and middle-income countries across five continents. There were significant regional differences in smoking cessation outcomes [18], with lower abstinence rates in, compared with outside, the United States (even after controlling for other factors).

This paper explores these findings from EAGLES, as, to our knowledge, no large-scale randomized controlled trials have examined global regional differences in predictors of smoking cessation outcomes among both high- and middle-income countries. Our first aim was to examine regional demographic, smoking, and psychiatric differences, and we hypothesized that significant baseline differences would be observed across regions. Our second aim was to

explore whether region- and country-specific variables – such as income, cigarette affordability, prevalence of tobacco use, and tobacco control policy – were associated with cessation outcomes. We hypothesized that participants from countries with more proactive tobacco control policies would have a less robust response to smoking cessation interventions than their counterparts due to possible "hardening."

METHODS

Design

This is a secondary analysis of data collected from the randomized, double-blind, triple-dummy, EAGLES trial (CinicalTrials.gov NCT01456936), which investigated the safety and efficacy of varenicline (1 mg twice daily) and bupropion (150 mg twice daily) in an active- (nicotine patch, 21 mg/day) and placebo-controlled study in 8144 smokers with (n=4116) and without (n=4028) psychiatric disorders. Participants received 12 weeks of active treatment (or placebo) and were followed for an additional 12 weeks, and all participants received brief cessation counseling. The primary outcome paper includes further details about study methodology and follows reporting recommendations set out by CONSORT guidelines [17, 19]. Briefly, eligible participants were stratified into a nonpsychiatric cohort (NPC) and four subcohorts (see below) in the psychiatric cohort (PC) based on their primary psychiatric diagnosis, and by site region across four prespecified geographical zones (United States, Western Europe and Other Countries, Eastern Europe, and South and Middle America). Treatment groups were balanced across the five diagnostic groups for each of the four regions. A computer-generated randomization schedule was used to assign participants to treatment using a block size of eight (1:1:1:1 ratio) for each of the diagnosis by region combinations.

Participants

Participants were male and female smokers, aged 18–75 years, who were motivated to quit smoking and smoked, on average, ≥10 cigarettes per day. Those in the psychiatric cohort (PC) met DSM-IV-TR [20] criteria for either 1) a mood disorder (major depressive or bipolar disorders); 2) anxiety disorder (panic, post-traumatic stress or obsessive compulsive disorder, social phobia or generalized anxiety disorder); 3) psychotic disorder (schizophrenia or schizoaffective disorder); or 4) borderline personality disorder as confirmed by the Structured Clinical Interview for the DSM-IV-TR for Axis I/II disorders (SCID-I/II) [21, 22]. Participants in the non-psychiatric cohort (NPC) had no history of mental illness, as confirmed by SCID-I/II. For this secondary analysis, we grouped countries into seven regions based on their geographic proximity and similarities in demographic characteristics (Table 2).

Table 2 Country-specific variables by region

Region	Country	Tobacco prevalence*	GDP *per capita*†	Cigarette relative income price‡	MPOWER score§
North America I	United States	21.5	55 048	1.1	22
	Canada	14.4	50 893	1.7	32
North America II	Mexico	14.7	10 922	3.1	26
South America	Argentina	22.0	12 335	1.4	33
	Brazil	14.4	12 113	2	34
	Chile	37.5	14 671	2	28
Eastern Europe	Bulgaria	33.4	7874	4.1	29
	Russian Federation	37.6	18 671	2	26
	Slovakia	28.9	14 096	1.2	30
Western Europe	Denmark	20.0	62 549	1.3	27
	Finland	18.7	50 260	1.5	29
	Germany	27.0	47 960	1.5	23
	Spain	26.0	29 462	2.2	30
Africa	South Africa	20.1	6433	4.5	14
Australasia	Australia	14.6	62 511	2.5	32
	New Zealand	15.3	44 553	3.2	28

* Tobacco smoking prevalence in 2015 [5].
† GDP *per capita* in 2014 (*per capita* in USD) [11].
‡ Relative cost of cigarettes as a percentage of GDP *per capita* required to purchase 2000 cigarettes of the most sold brand [1].
§ MPOWER policy score in 2015 (out of 37) [2].
GDP, gross domestic product; USD, United States dollars.

Primary outcome measure

The primary outcome for this secondary analysis was 7-day point prevalence abstinence (PPA) at the end of treatment (week 12) defined as self-reported no smoking for one week confirmed by expired breath carbon monoxide levels < 10 parts per million at that study visit. This endpoint was selected to amplify the abstinence signal as early abstinence has been shown to strongly predict future long-term abstinence [23].

EAGLES independent variables

Participant characteristics associated with continuous abstinence from 9 to 24 weeks were included as candidate predictor terms in this secondary analysis [18]. These included age, gender, body mass index (BMI), race (White vs non-White), nicotine dependence severity (measured by Fagerström Test for Cigarette Dependence [FTCD]) [24], cigarettes per day in the month prior to enrollment, prior use of smoking cessation medications (varenicline, bupropion, or nicotine replacement therapy [NRT]), age when started smoking, lives with smoker and has contact with smokers. Additionally, we included seven mental health characteristics: comorbid psychiatric diagnosis (none, mood disorder, anxiety disorder, psychotic disorder) [20]; depression symptom severity (measured by Hospital Anxiety and Depression Scale [HADS]) [25]; anxiety symptom severity (measured by HADS) [25]; aggression symptom severity (measured by Buss–Perry Aggression Questionnaire) [26]; lifetime suicidal behavior and/or ideation (yes/no, measured by Columbia–Suicide Severity Rating Scale) [27]; comorbid alcohol

or other substance dependence (defined by DSM-IV-TR and confirmed by SCID-I/II) [20]; and use of psychotropic medication (yes/no).

Non-EAGLES country-level independent variables

Four country-specific variables were sourced to reflect their values during the period in which EAGLES was conducted (2011–2015) (Table 1).

Baseline tobacco smoking prevalence was extracted from WHO statistics on smoking prevalence rates from 2015 [5]. To measure the regional economic influence on cessation outcomes, both absolute and relative measures were obtained. The gross domestic product (GDP) of each country was measured as GDP *per capita* in US dollars in 2014 (as reported by the World Bank) [11], which was then divided by 10 000 to facilitate effect interpretation. To look at the affordability of cigarettes in a country, we use the "relative income price" (RIP) measure, calculated as the percentage of GDP *per capita* required to purchase 2000 cigarettes (100 packs) of the most sold brand (data from 2014 [5]).

The rigor of each country's tobacco control policy was estimated using the WHO's 37-point MPOWER score, which quantifies the degree of implementation and enforcement of the FCTC. Points are awarded according to six core domains (Table 1) [12]. A higher score indicates greater adherence to FCTC guidelines, with a maximum possible score of 37. Table 2 illustrates the country-level variables (tobacco prevalence, GDP, cigarette RIP, and MPOWER score) we derived for all 16 countries in which EAGLES participants were enrolled. It further depicts the seven geographic regions we characterized to capture these regional differences. Each EAGLES participant was assigned values for these four variables corresponding to the location of their respective study site.

Statistical analysis

Descriptive statistics were compiled to examine baseline differences by country and geographic region, with respect to demographic, smoking, and mental health characteristics. A correlation assessment for the country-level variables was reviewed to alleviate any multicollinearity concerns with these measures. For the primary efficacy endpoint of 7-day PPA at week 12, model building used a stepwise, logistic regression analysis. Significance levels were set *a priori* as 10% for a variable to enter and 15% to remain in the model. The method forced inclusion of treatment condition (placebo, varenicline, bupropion, NRT) and cohort (PC and NPC). Main-effect candidates included regions (7-level), four country-level non-EAGLES variables, and 17 EAGLES baseline characteristics, described above. All randomized subjects were included, with odds ratios [ORs] (95% confidence intervals [CIs]) computed.

Patient and public involvement

None.

RESULTS

Smoking prevalence rates varied widely across the countries and regions represented in EAGLES (Table 3). Smoking rates were highest in the Russian Federation and Eastern Europe. Australia, Brazil, Canada, and Mexico had smoking prevalence rates below 15%. There was also marked variability in countries' GDP, with Denmark and Australia registering as the highest income countries, and South Africa and Bulgaria as the lowest among EAGLES countries. Relative cost of cigarettes was highest in South Africa and Bulgaria; the United States had the

lowest cigarette RIP in 2014. MPOWER scores ranged from a low of 14 in South Africa to a high of 34 in Brazil. These four variables were not significantly correlated (data not shown).

Mean tobacco smoking prevalence was highest in Eastern Europe (32.8%) and tied for lowest in Australasia and North America II (Mexico) (15.0%). Although North America II (Mexico) had the lowest proportion of participants with psychiatric diagnosis and no active substance use disorders, participants enrolled in this country had the highest baseline levels of anxiety (5.8 ± 4.1), depression (3.7 ± 3.2), and aggression (62.2± 17.8) scores. South Africa had the lowest GDP *per capita* (6433 ± 0.0) and lowest MPOWER policy score (14.0 ± 0.0). South America had the highest MPOWER score (32.8 ± 1.1).

Table 3 Baseline characteristics by region (demographic, smoking, psychiatric, and country-level variables)

Variable		All (N=8144)	North America I (n=4539)	North America II (n=188)	South America (n=371)	Eastern Europe (n=818)	Western Europe (n=1750)	Africa (n=296)	Australasia (n=182)
Demographic characteristics									
Age, years, mean (SD)		46.5 (12.3)	46.5 (12.4)	47.6 (11.7)	51.7 (11.2)	42.9 (11.8)	48.1 (11.5)	41.3 (13.7)	43.2 (13.8)
Race	White	6649 (81.6)	3304 (72.8)	184 (97.9)	368 (99.2)	818 (100)	1736 (99.2)	116 (39.2)	123 (67.6)
	Black	1162 (14.2)	1071 (23.6)	1 (0.5)	2 (0.5)	0 (0)	2 (0.1)	86 (29.1)	0 (0)
	Other	332 (4.1)	163 (3.6)	3 (1.6)	1 (0.3)	0 (0)	12 (0.7)	94 (31.8)	59 (32.4)
Gender	Male	3592 (44.1)	1907 (42.0)	93 (49.5)	169 (45.6)	394 (48.2)	790 (45.1)	166 (56.1)	73 (40.1)
	Female	4552 (55.9)	2632 (58.0)	95 (50.5)	202 (54.4)	424 (51.8)	960 (54.9)	130 (43.9)	109 (59.9)
Smoking characteristics									
FTCD score, mean (SD)		5.8 (2.0)	5.7 (1.9)	5.5 (2.1)	5.5 (2.3)	6.2 (2.1)	5.8 (2.0)	5.1 (1.9)	5.5 (2.0)
Cigarettes per day in past month, mean (SD)		20.7 (8.2)	19.5 (7.7)	19.5 (7.7)	26.6 (11.4)	23.1 (8.1)	21.7 (7.9)	19.1 (9.2)	18.9 (7.0)
Living with smoker		2931 (36.0)	1655 (36.5)	69 (36.7)	134 (36.1)	398 (48.7)	486 (27.8)	125 (42.2)	64 (35.2)
Prior treatment	Prior varenicline use	1271 (15.6)	934 (20.6)	7 (3.7)	10 (2.7)	1 (0.1)	236 (13.5)	18 (6.1)	65 (35.7)
	Prior bupropion use	844 (10.4)	640 (14.1)	1 (0.5)	17 (4.6)	0 (0)	127 (7.3)	39 (13.2)	20 (11.0)
	Prior NRT use	2136 (26.2)	1551 (34.2)	9 (4.8)	3 (0.8)	27 (3.3)	450 (25.7)	20 (6.8)	76 (41.8)
Psychiatric characteristics									
Comorbid psychiatric diagnosis		1511 (18.6)	1092 (24.1)	2 (1.1)	42 (11.3)	13 (1.6)	282 (16.1)	31 (10.5)	49 (26.9)
No primary mood disorder		4028 (49.5)	2037 (44.9)	134 (71.3)	243 (65.5)	446 (54.5)	843 (48.2)	225 (76.0)	100 (54.9)
Primary mood disorder		2910 (35.7)	1883 (41.5)	44 (23.4)	50 (13.5)	138 (16.9)	691 (39.5)	56 (18.9)	48 (26.4)
Primary anxiety disorder		792 (9.7)	424 (9.3)	6 (3.2)	69 (18.6)	110 (13.4)	156 (8.9)	4 (1.4)	23 (12.6)

Variable	All (N=8144)	North America I (n=4539)	North America II (n=188)	South America (n=371)	Eastern Europe (n=818)	Western Europe (n=1750)	Africa (n=296)	Australasia (n=182)
Primary psychotic disorder	390 (4.8)	193 (4.3)	2 (1.1)	4 (1.1)	121 (14.8)	49 (2.8)	10 (3.4)	11 (6.0)
Borderline personality disorder	24 (0.3)	2 (<0.1)	2 (1.1)	5 (1.3)	3 (0.4)	11 (0.6)	1 (0.3)	0 (0)
HADS anxiety score, mean (SD)	4.0 (3.6)	4.2 (3.6)	5.8 (4.1)	3.4 (2.9)	2.2 (2.7)	4.2 (3.5)	3.7 (3.7)	4.6 (3.5)
HADS depression score, mean (SD)	2.4 (2.9)	2.4 (2.9)	3.7 (3.2)	2.1 (2.5)	2.0 (2.6)	2.4 (3.1)	2.2 (2.5)	2.3 (2.8)
Aggression Q total score, mean (SD)	55.5 (17.4)	54.5 (18.2)	62.2 (17.8)	62.2 (17.1)	55.2 (15.7)	55.5 (15.7)	57.3 (17.2)	56.6 (17.0)
C-SSRS BEID	1623 (19.9)	1010 (22.3)	37 (19.7)	25 (6.7)	14 (1.7)	430 (24.6)	97 (33.5)	67 (36.8)
Alcohol/substance dependence/use	957 (11.8)	778 (17.1)	0 (0)	12 (3.2)	5 (0.6)	109 (6.2)	33 (11.7)	36 (19.8)
Any psychotropic medication use	2325 (28.5)	1459 (32.1)	22 (11.7)	80 (21.6)	294 (35.9)	377 (21.5)	51 (17.2)	42 (23.1)
Newly derived country-specific variables								
Tobacco prevalence, mean (SD)	22.9 (4.6)	21.5 (1.9)	15.0 (0.0)	22.3 (3.9)	32.8 (2.8)	24.1 (3.7)	20.0 (0.0)	15.0 (0.0)
GDP, mean (SD)	43 972.4 (17 700.4)	54 792.6 (998.1)	10 922.0 (0.0)	12 429.5 (494.5)	11 498.7 (4651.8)	47 028.9 (7833.6)	3433.0 (0.0)	50 177.2 (8351.7)
Cigarette RIP, mean (SD)	1.7 (1.0)	1.1 (0.1)	3.1 (0.0)	1.5 (0.2)	3.1 (1.2)	1.6 (0.3)	3.5 (0.0)	3.0 (0.3)
MPOWER score, mean (SD)	24.3 (4.2)	22.6 (2.4)	26.0 (0.0)	32.8 (1.1)	28.4 (1.4)	25.9 (3.1)	24.0 (0.0)	29.3 (1.9)

All data are given as n (%) unless otherwise specified.

BEID, behavior and/or ideation; C-SSRS, Columbia–Suicide Severity Rating Scale; FTCD, Framework Convention on Tobacco Control; GDP, gross domestic product; HADS, Hospital Anxiety and Depression Scale; NRT, nicotine replacement therapy; Q, questionnaire; RIP, relative income price; SD, standard deviation.

Seven-day end-of-treatment PPA varied widely across regions (Figure 1), with the lowest rates found in Australasia (22.0%) and North America I (22.5%) and the highest rate (55.9%) in North America II (Mexico).

Table 4 depicts the results of the stepwise regression model examining the association of the 17 candidate predictor variables and the primary endpoint of 7-day PPA. Consistent with prior analyses of EAGLES data, individuals of Black compared to White race (OR 0.622 [95% CI 0.518, 0.748]), with psychotic disorders (0.605 [0.435, 0.841]), psychiatric medication use (0.789 [0.688, 0.904]), more cigarettes per day (0.968 [0.960, 0.976]) and contact with a smoker (0.856 [0.764, 0.961]) had lower odds of achieving short-term abstinence. Higher abstinence rates were observed in older participants (OR 1.010 [95% CI 1.005, 1.014]), with greater BMI (1.013 [1.004, 1.022]) and with prior varenicline use (1.228 [1.060, 1.422]). Additionally, all treatment groups demonstrated higher odds of abstinence as compared to placebo, as follows: varenicline (OR 3.808 [95% CI 3.260, 4.447]), bupropion (2.059 [1.755, 2.417]) and NRT (2.103 [1.793, 2.468]).

Table 4 Main-effect odds ratios for final stepwise logistic regression model of 7-day PPA, week 12

Effect*		Odds ratio estimate	95% lower CI	95% upper CI
Demographics	Age	1.010	1.005	1.014
	BMI	1.013	1.004	1.022
	Black race (vs White)	0.622	0.518	0.748
Psychiatric characteristics	Psychotic disorder	0.605	0.435	0.841
	Use of psychiatric medications	0.789	0.688	0.904
Smoking characteristics	FTND	0.907	0.879	0.936
	Cigarettes per day	0.968	0.960	0.976
	Contact with smoker	0.856	0.764	0.961
	Prior varenicline	1.228	1.060	1.422
Treatment group (vs placebo)	Varenicline	3.808	3.260	4.447
	Bupropion	2.059	1.755	2.417
	NRT	2.103	1.793	2.468

Region (vs North America I)	Eastern Europe	0.390	0.222	0.686
	South America	0.170	0.083	0.348
	Western Europe	1.356	1.140	1.613
Country-level variables	GDP†	0.544	0.468	0.631
	Cigarette RIP	0.617	0.528	0.722
	MPOWER	1.031	1.008	1.055

BMI, body mass index; CL, confidence interval; FTND, Fagerström Test for Nicotine Dependence; GDP, gross domestic product; NRT, nicotine replacement therapy; PPA, point prevalence abstinence; RIP, relative income price.

* Only most significant effects shown.

† GDP *per capita* per $10,000 USD.

After controlling for those traditional predictor variables, region remained in the model as a significant main effect. Using North America I (United States and Canada) as the referent, odds of achieving short-term abstinence were significantly higher in the Western European (OR 1.356 [95% CI 1.140, 1.613]) and lower in the Eastern European (0.390 [0.222, 0.686]) and South American (0.170 [0.083, 0.348]) regions.

Of the four country-level variables, three predicted abstinence (Table 4). Lower odds of abstinence were seen with higher GDP (OR 0.544 [95% CI 0.468, 0.631]) and higher cigarette RIP (0.617 [0.528, 0.722]), whereas higher odds were seen with higher MPOWER score (1.031 [1.008, 1.055]). Notably, tobacco smoking prevalence was not included in the model.

DISCUSSION

As predicted, individual-level variables of demographic, psychiatric, and smoking-related characteristics, as well as country-level variables of income, cigarette relative income price, and implementation of tobacco control policy, were associated with the likelihood of quitting. Specifically, the higher the income of a country and the more expensive cigarettes relative to a country's per capita GDP, the lower the likelihood of abstinence at end of treatment. Conversely, more stringent tobacco control policy implementation was associated with increased rates of

abstinence. Finally, country-level tobacco prevalence at the time the EAGLES study was conducted was not significantly correlated with abstinence initiation rates. After controlling for these and other traditional predictor variables, global region was still found to be a significant independent predictor of short-term smoking abstinence.

Despite adhering to the same study protocol with standardized inclusion and exclusion criteria used to enroll smoking participants, baseline characteristics by region differed broadly across the board with respect to age, gender, race, psychiatric history, psychiatric symptoms, prior treatments, severity of tobacco use and dependence, and substance use history. For instance, participants enrolled in the South American region were the oldest, smoked the most cigarettes per day, and were 99% White; Africa was the only region where males predominated and participants were predominantly non-White. Some regions had a substantial number of participants who had previously tried smoking cessation treatments, but regions such as Eastern Europe and North America II (Mexico) had hardly any. These individual-level characteristics have been shown to be independently associated with tobacco cessation outcomes, both in our earlier analysis [18] and in the literature more generally [13, 23, 28]. There is a growing body of literature suggesting the benefit of interventions specific to these risk factors [29-31], and one might extrapolate a potential benefit in tailoring a region's tobacco control plan to its unique characteristic makeup.

We found that a greater degree of tobacco control policy implementation, as reflected by higher MPOWER scores, was associated with higher odds of achieving short-term abstinence in EAGLES. This suggests that greater tobacco regulation is associated with higher quit rates, which is corroborated by the literature [32] and aligns with the greater mission of the FCTC. Although it may be presumed that greater tobacco control would be found in higher-income

regions and reflected by higher-priced and taxed cigarettes, our analysis did not find that to be the case. In fact, not only did we *not* find a correlation between those variables, but we found an inverse relationship with cessation rates. Our analysis found that higher income and more expensive cigarettes (i.e., higher RIP) were associated with lower cessation rates. This paradox comes as a surprise among the growing body of literature reporting that higher-income countries have had more drastic reductions in smoking prevalence [5], thought to be due to greater funding for and access to cessation interventions [33]. However, a newer, large-scale global analysis, published by Sathish *et al* [34], found that smokers in high-income countries were consuming cigarettes with much higher levels of nicotine than those in middle- or lower-income countries, which might make it harder to quit [34]. The literature also supports the idea that increasing the price of cigarettes is associated with a greater likelihood of quitting [6, 35], which is in opposition to our finding. But here again, as demonstrated in South Africa [36], raising prices on cigarettes via taxes may inadvertently lead to a proliferation of illicit cigarettes and the introduction of cheaper local brands, which may undermine tobacco regulatory efforts.

One possible explanation for these curious results is the controversial "hardening hypothesis" that smokers who find it easier to quit have already done so, leaving "hardened" smokers. If someone continues to smoke cigarettes despite the increasing cost, that individual may fall under the umbrella of a "hardened" smoker, and thus have more difficulty quitting. The same may apply to higher-income regions, with presumed greater access to healthcare and cessation resources. However, hardening is commonly attributed to populations with lower smoking prevalence [14-16], and in our analysis, a region's smoking prevalence rate at the time EAGLES was conducted was not a significant predictor of smoking cessation success once other variables were included in the model. Basing the hardening hypothesis purely on smoking

prevalence at a single time point is likely too reductionist a model. For example, Cheung *et al* found a model that may unite contradictory findings about hardening [37]. Their sample showed a U-shaped relationship between the odds of quitting smoking and smoking prevalence, in which odds of quitting were highest at either extreme of the smoking prevalence curve.

Even though we examined these regional effects in a more granular, seven-region context compared with our prior EAGLES analyses, which considered only a US/non-US dichotomy, the region from which subjects were enrolled remained a significant main effect in the analytic model despite also controlling for treatment group and psychiatric subcohort. The EAGLES dataset was not intended to represent the global population of smokers at large, nor was its enrollment strategy designed to randomize participants within each of the countries participating. Nevertheless, our regional findings appeared to have similar trends to others described in the literature. Our prior work [13] did not make the distinction between Eastern and Western Europe, but found that European smokers had higher rates of abstinence overall compared with US smokers. In our current analysis, we found that, when compared to North American I (United States and Canada) participants, smokers enrolled in the Western European region had approximately one-third higher odds of abstinence, whereas enrollees in Eastern Europe had less than half the odds of quitting. The literature supports this finding, and when compared to Western Europe, Eastern Europe has been found to have lower smoking cessation rates [38], higher smoking prevalence rates, and higher rates of morbidity and mortality attributable to tobacco [5]. These challenges are thought to be due to more accessible cigarettes, less tobacco control, and particular cultural and religious practices in the region [5]. We also found that smokers enrolled at sites in South America had the lowest odds of successful cessation – about one-quarter of the odds in North America I (Table 4). A 2008 review paper from Muller and

Wehbe [39] examined unique factors in Latin America that contribute to its growing tobacco epidemic, particularly that this region includes some of the highest tobacco-producing countries in the world (in our dataset, Brazil #3 and Argentina #9), and that such an economic reliance on tobacco products has likely contributed to less rigorous tobacco control, less expensive cigarettes, and an ongoing tobacco smuggling trade [39]. It is curious then, in our analysis, that this region had the *highest* MPOWER score. Because our model was designed to include all regions, each predictor might not extrapolate to each individual region.

Our analyses were not without limitations. The EAGLES trial was not designed to recruit representative samples of a country's smokers, but rather, to enroll smokers who met prespecified inclusion/exclusion criteria into a methodologically sound, randomized controlled trial comparing the first-line smoking cessation medications and placebo. Thus, the results might not generalize to the global population of smokers at large and may not be representative of each country's smokers. Sites enrolling participants in EAGLES were located primarily in high- and upper-middle income countries, further limiting generalizability. Over half the EAGLES participants were enrolled in the United States, an imbalance that could have affected results. Although we controlled for treatment condition and psychiatric cohort in our analyses and examined correlations among the newly introduced country-level variables, we cannot rule out multicollinearity among predictor variables affecting the results. Moreover, we did not assess how sociocultural factors, including differences in stigma levels surrounding reporting mental health conditions across countries, may have influenced results. Nonetheless, EAGLES remains the largest, most rigorous, placebo-controlled, multinational trial of smoking cessation medications ever conducted, and the new results obtained will help inform subsequent analyses in samples more representative of smokers across the globe.

In conclusion, geographic region had a significant effect on the odds of achieving short-term smoking abstinence in EAGLES even after controlling for treatment, psychiatric comorbidity, individual-level, and country-specific variables. Increased tobacco control policy and enforcement was associated with greater chance of achieving short-term abstinence, which supports the argument that tighter regulation is associated with enhanced efficacy of smoking cessation treatments. Although seemingly contradictory, increased income of a country and more expensive cigarettes were associated with lower odds of abstinence, which might reflect hardening of smokers in those countries. The literature remains mixed about whether hardening truly exists; it may be that a deeper understanding of this complex phenomenon is needed, rather than refuting the validity of the hypothesis itself.

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Contributors AEE and RMA were involved in the conception and design of the parent study; BD, DEL, BSM, PS, TM, AEE and RMA were involved with the *post-hoc* analyses and/or interpretation of the data. DEL performed the statistical analyses. RMA and DEL are responsible for the overall content as guarantor. All authors were involved in the drafting of the manuscript and revising it critically for intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Ethics approval EAGLES was reviewed and approved by each site's institutional review board or ethics committee and was conducted in accordance with the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines.

Data availability statement Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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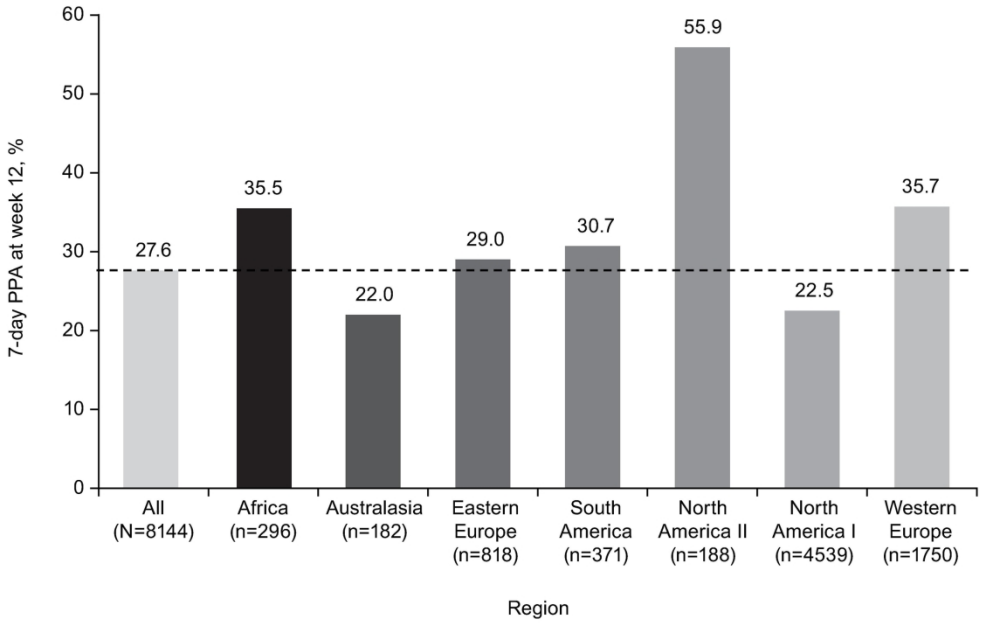
<FIGURE LEGEND>

Figure 1 Seven-day PPA at week 12 by region. All patients randomized. PPA, point prevalence abstinence.



Seven-day PPA at week 12 by region. All patients randomized. PPA, point prevalence abstinence.

180x118mm (300 x 300 DPI)

Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	3
Introduction			

Background and objectives	#2a	Scientific background and explanation of rationale	5-6
Background and objectives	#2b	Specific objectives or hypothesis	7-8
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	8*
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	8*
Participants	#4a	Eligibility criteria for participants	8-9
Participants	#4b	Settings and locations where the data were collected	7-8*
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8*
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	9-10
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	8*
Sample size	#7a	How sample size was determined.	8*

Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	8*
			8*
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size) - 8*	
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8*
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	8*
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	8*
Blinding	#11b	If relevant, description of the similarity of interventions	8*
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	11-12

Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11-12
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8*
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	8*
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	8*
Recruitment	#14b	Why the trial ended or was stopped	8*
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	14-15
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8*
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16-17
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	15-16

Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8*
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	8*
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	21
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-20
Registration	#23	Registration number and name of trial registry	8
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-20
Registration	#23	Registration number and name of trial registry	8
Protocol	#24	Where the full trial protocol can be accessed, if available	8*
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	23

*Referenced in the paper but more explicitly elaborated in primary outcome paper (Anthenelli RM, Benowitz NL, West R, *et al.* Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387:2507-20)

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Do tobacco regulatory and economic factors influence smoking cessation outcomes? A post-hoc analysis of the multinational EAGLES randomized controlled trial

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Do tobacco regulatory and economic factors influence smoking cessation outcomes? A post-hoc analysis of the multinational EAGLES randomized controlled trial

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ABSTRACT

Introduction We previously reported global regional differences in smoking cessation outcomes, with smokers of United States origin having lower quit rates than smokers from some other countries. This post hoc analysis examined global regional differences in individual- and country-level epidemiologic, economic, and tobacco regulatory factors that may affect cessation outcomes.

Methods EAGLES (NCT01456936) was a randomized controlled trial that evaluated first-line cessation medications and placebo in 8144 smokers with and without psychiatric disorders from 16 countries across seven regions. Generalized linear and stepwise logistic regression models that considered pharmacotherapy treatment, psychiatric diagnoses, traditional individual-level predictors (e.g., demographic and smoking characteristics), and country-specific smoking prevalence rates, gross domestic product (GDP) per capita, relative cigarette cost, and WHO-derived MPOWER scores were used to predict 7-day point prevalence abstinence at the end of treatment.

Results In addition to several traditional predictors, three of four country-level variables predicted short-term abstinence: GDP (0.54 [95% CI 0.47, 0.63]), cigarette relative income price (0.62 [0.53, 0.72]), and MPOWER score (1.03 [1.01, 1.06]). Quit rates varied across regions (22.0% in Australasia to 55.9% in Mexico). With northern North America (United States and Canada) as the referent, the likelihood of achieving short-term abstinence was significantly higher in Western Europe (OR 1.4 [95% CI 1.14, 1.61]), but significantly lower in Eastern Europe (0.39 [0.22, 0.69]) and South America (0.17 [0.08, 0.35]).

Conclusions Increased tobacco regulation was associated with enhanced quitting among participants in the EAGLES trial. Paradoxically, lower GDP, and more affordable cigarette

pricing relative to a country's GDP, were also associated with higher odds of quitting. Geographic region was also a significant independent predictor.

Strengths and limitations of this study

- EAGLES is the largest randomized, placebo-controlled trial of cessation medications that enrolled persons with and without psychiatric disorders who smoke in 16 high- and middle-income countries across five continents
- The present *post-hoc* analysis of EAGLES trial results extends prior work by incorporating novel country- and region-specific factors as predictors of smoking cessation outcomes
- The EAGLES trial was not designed to recruit representative samples of a country's smokers; but rather, to enroll smokers who met prespecified inclusion/exclusion criteria, which may limit generalizability

INTRODUCTION

An estimated 1.3 billion (roughly 1 in 5) people worldwide use tobacco [1]. Although global smoking prevalence is decreasing [2], the number of smokers continues to increase [2]. Smoking is the leading cause of preventable death worldwide [3]. Tobacco-related deaths are increasing [2], with more than 8 million deaths per year attributable to tobacco [1].

As of 2017, high-income countries still had higher smoking prevalence rates (21.6%) than low- (11.2%) and middle-income (19.5%) countries [4]. However, high-income countries also show disproportionately greater reductions in smoking prevalence than low- and middle-income countries [5]. As a result, low- to middle-income countries are now home to 80% of the world's population of smokers [1] and report the majority of tobacco-related deaths [6].

Smoking prevalence also varies greatly by geographic region. According to the World Health Organization (WHO) prevalence estimates for 2015, the European region had the highest smoking rates (29.9%), followed by the Western Pacific region (24.8%); the African region had the lowest (10.0%) [4]. Although smoking prevalence is decreasing (and expected to continue decreasing) in most regions, the eastern Mediterranean is projected to be an exception [6].

In 2003, to address these disparities, WHO established the Framework Convention on Tobacco Control (FCTC), which outlines policies and measures to promote tobacco use prevention and treatment globally [7]. To track the progress of individual countries, WHO developed a quantitative measure – the MPOWER score. This grades a country's tobacco control efforts across six domains (Table 1). Countries with higher MPOWER scores showed greater reduction in smoking prevalence over the first decade of FCTC implementation [8]. However, regional disparities in overall tobacco use prevalence cannot be fully addressed without understanding the contributors to such disparities, specifically whether these could also be

influencing regional cessation rates. Individual-level predictors of smoking cessation are widely studied in the literature. Fewer studies have explored how country of origin might influence abstinence. The International Tobacco Control Four Country Survey (ITC-4) was a large prospective cohort study that involved telephone surveys of more than 2000 smokers in Australia, Canada, the United Kingdom, and the United States. An analysis of the ITC-4 data by Hyland *et al* [9] demonstrated that these countries' smoking cessation rates were not equally moderated by traditional individual predictors such as the Heaviness of Smoking Index, and favorable attitudes about smoking and self-efficacy for quitting. Furthermore, heaviness of smoking was associated with lower income in all countries but the United States [10].

Table 1 Country-level economic, epidemiologic, and policy variables

Tobacco prevalence	Tobacco smoking prevalence in 2015 [5]
GDP *per capita*	GDP *per capita* in US dollars in 2014 [11]
Cigarette relative income price	Relative cost of cigarettes calculated as percentage of GDP *per capita* required to purchase 2000 cigarettes of the most sold brand in 2014 [5]
MPOWER score	A quantitative measure of tobacco control policy developed by the World Health Organization to support policy implementation under the Framework Convention on Tobacco Control [12]. It is based on a composite score (out of a total of 37) of six core measures: **M** = Monitoring tobacco use and prevention policies **P** = Protecting people from tobacco smoke **O** = Offering help to quit tobacco use **W** = Warning about the dangers of tobacco **E** = Enforcing bans on tobacco advertising, promotion and sponsorship **R** = Raising taxes on tobacco

GDP, gross domestic product.

Our prior work similarly noted regional effects on smoking cessation rates, while also incorporating the impact of pharmacotherapy. One secondary analysis of a study examining the effect of varenicline on depressed smokers demonstrated that European participants were four times more likely to achieve abstinence than US participants, and that higher levels of baseline depressive symptoms were associated with lower abstinence rates for European but not US participants [13].

One proposed explanation for these results is the "hardening hypothesis" – that areas with lower smoking prevalence are composed of more "hardened" smokers who have greater difficulty quitting. Smokers who found it easier to quit have already quit, and the remaining hardened smokers are more nicotine dependent, of lower socioeconomic status, and have greater likelihood of psychiatric comorbidity [14]. This hypothesis has been difficult to consistently support [14-16]. A major gap within the "hardening" literature is that most studies have been conducted in high-income countries [14]. If hardening were to be demonstrated on a broader global scale, there could be significant implications for international tobacco policy.

Similar limitations exist in the literature on predictors of smoking cessation: regional differences are primarily examined among high-income, Westernized countries. Fewer studies include geographically and economically diverse countries. Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) was a large-scale, multinational, randomized, placebo-controlled, smoking cessation pharmacotherapy study, conducted from 2011 to 2015, that offered a unique opportunity to examine smoking cessation outcomes on a global level [17]. Participants were recruited from 16 high- and middle-income countries across five continents. There were significant regional differences in smoking cessation outcomes [18], with lower abstinence rates in, compared with outside, the United States (even after controlling for other factors).

This paper explores these findings from EAGLES, as, to our knowledge, no large-scale randomized controlled trials have examined global regional differences in predictors of smoking cessation outcomes among both high- and middle-income countries. Our first aim was to examine regional demographic, smoking, and psychiatric differences, and we hypothesized that significant baseline differences would be observed across regions. Our second aim was to

explore whether region- and country-specific variables – such as income, cigarette affordability, prevalence of tobacco use, and tobacco control policy – were associated with cessation outcomes. We hypothesized that participants from countries with more proactive tobacco control policies would have a less robust response to smoking cessation interventions than their counterparts due to possible "hardening."

METHODS

Design

This is a secondary analysis of data collected from the randomized, double-blind, triple-dummy, EAGLES trial (CinicalTrials.gov NCT01456936), which investigated the safety and efficacy of varenicline (1 mg twice daily) and bupropion (150 mg twice daily) in an active- (nicotine patch, 21 mg/day) and placebo-controlled study in 8144 smokers with (n=4116) and without (n=4028) psychiatric disorders. Participants received 12 weeks of active treatment (or placebo) and were followed for an additional 12 weeks, and all participants received brief cessation counseling. The primary outcome paper includes further details about study methodology and follows reporting recommendations set out by CONSORT guidelines [17, 19]. Briefly, eligible participants were stratified into a nonpsychiatric cohort (NPC) and four subcohorts (see below) in the psychiatric cohort (PC) based on their primary psychiatric diagnosis, and by site region across four prespecified geographical zones (United States, Western Europe and Other Countries, Eastern Europe, and South and Middle America). Treatment groups were balanced across the five diagnostic groups for each of the four regions. A computer-generated randomization schedule was used to assign participants to treatment using a block size of eight (1:1:1:1 ratio) for each of the diagnosis by region combinations.

Participants

Participants were male and female smokers, aged 18–75 years, who were motivated to quit smoking and smoked, on average, ≥10 cigarettes per day. Those in the psychiatric cohort (PC) met DSM-IV-TR [20] criteria for either 1) a mood disorder (major depressive or bipolar disorders); 2) anxiety disorder (panic, post-traumatic stress or obsessive compulsive disorder, social phobia or generalized anxiety disorder); 3) psychotic disorder (schizophrenia or schizoaffective disorder); or 4) borderline personality disorder as confirmed by the Structured Clinical Interview for the DSM-IV-TR for Axis I/II disorders (SCID-I/II) [21, 22]. Participants in the non-psychiatric cohort (NPC) had no history of mental illness, as confirmed by SCID-I/II. For this secondary analysis, we grouped countries into seven regions based on their geographic proximity and similarities in demographic characteristics (Table 2).

Table 2 Country-specific variables by region

Region	Country	Tobacco prevalence*	GDP *per capita*†	Cigarette relative income price‡	MPOWER score§
North America I	United States	21.5	55 048	1.1	22
	Canada	14.4	50 893	1.7	32
North America II	Mexico	14.7	10 922	3.1	26
South America	Argentina	22.0	12 335	1.4	33
	Brazil	14.4	12 113	2	34
	Chile	37.5	14 671	2	28
Eastern Europe	Bulgaria	33.4	7874	4.1	29
	Russian Federation	37.6	18 671	2	26
	Slovakia	28.9	14 096	1.2	30
Western Europe	Denmark	20.0	62 549	1.3	27
	Finland	18.7	50 260	1.5	29
	Germany	27.0	47 960	1.5	23
	Spain	26.0	29 462	2.2	30
Africa	South Africa	20.1	6433	4.5	14
Australasia	Australia	14.6	62 511	2.5	32
	New Zealand	15.3	44 553	3.2	28

* Tobacco smoking prevalence in 2015 [5].
† GDP *per capita* in 2014 (*per capita* in USD) [11].
‡ Relative cost of cigarettes as a percentage of GDP *per capita* required to purchase 2000 cigarettes of the most sold brand [1].
§ MPOWER policy score in 2015 (out of 37) [12].
GDP, gross domestic product; USD, United States dollars.

Primary outcome measure

The primary outcome for this secondary analysis was 7-day point prevalence abstinence (PPA) at the end of treatment (week 12) defined as self-reported no smoking for one week confirmed by expired breath carbon monoxide levels < 10 parts per million at that study visit. This endpoint was selected to amplify the abstinence signal as early abstinence has been shown to strongly predict future long-term abstinence [23].

EAGLES independent variables

Participant characteristics associated with continuous abstinence from 9 to 24 weeks were included as candidate predictor terms in this secondary analysis [18]. These included age, gender, body mass index (BMI), race (White vs non-White), nicotine dependence severity (measured by Fagerström Test for Cigarette Dependence [FTCD]) [24], cigarettes per day in the month prior to enrollment, prior use of smoking cessation medications (varenicline, bupropion, or nicotine replacement therapy [NRT]), age when started smoking, lives with smoker and has contact with smokers. Additionally, we included seven mental health characteristics: comorbid psychiatric diagnosis (none, mood disorder, anxiety disorder, psychotic disorder) [20]; depression symptom severity (measured by Hospital Anxiety and Depression Scale [HADS]) [25]; anxiety symptom severity (measured by HADS) [25]; aggression symptom severity (measured by Buss–Perry Aggression Questionnaire) [26]; lifetime suicidal behavior and/or ideation (yes/no, measured by Columbia–Suicide Severity Rating Scale) [27]; comorbid alcohol

or other substance dependence (defined by DSM-IV-TR and confirmed by SCID-I/II) [20]; and use of psychotropic medication (yes/no).

Non-EAGLES country-level independent variables

Four country-specific variables were sourced to reflect their values during the period in which EAGLES was conducted (2011–2015) (Table 1).

Baseline tobacco smoking prevalence was extracted from WHO statistics on smoking prevalence rates from 2015 [5]. To measure the regional economic influence on cessation outcomes, both absolute and relative measures were obtained. The gross domestic product (GDP) of each country was measured as GDP *per capita* in US dollars in 2014 (as reported by the World Bank) [11], which was then divided by 10 000 to facilitate effect interpretation. To look at the affordability of cigarettes in a country, we use the "relative income price" (RIP) measure, calculated as the percentage of GDP *per capita* required to purchase 2000 cigarettes (100 packs) of the most sold brand (data from 2014 [5]).

The rigor of each country's tobacco control policy was estimated using the WHO's 37-point MPOWER score, which quantifies the degree of implementation and enforcement of the FCTC. Points are awarded according to six core domains (Table 1) [12]. A higher score indicates greater adherence to FCTC guidelines, with a maximum possible score of 37. Table 2 illustrates the country-level variables (tobacco prevalence, GDP, cigarette RIP, and MPOWER score) we derived for all 16 countries in which EAGLES participants were enrolled. It further depicts the seven geographic regions we characterized to capture these regional differences. Each EAGLES participant was assigned values for these four variables corresponding to the location of their respective study site.

Statistical analysis

Descriptive statistics were compiled to examine baseline differences by country and geographic region, with respect to demographic, smoking, and mental health characteristics. A correlation assessment for the country-level variables was reviewed to alleviate any multicollinearity concerns with these measures. For the primary efficacy endpoint of 7-day PPA at week 12, model building used a stepwise, logistic regression analysis. Significance levels were set *a priori* as 10% for a variable to enter and 15% to remain in the model. The method forced inclusion of treatment condition (placebo, varenicline, bupropion, NRT) and cohort (PC and NPC). Main-effect candidates included regions (7-level), four country-level non-EAGLES variables, and 17 EAGLES baseline characteristics, described above. All randomized subjects were included, with odds ratios [ORs] (95% confidence intervals [CIs]) computed.

Patient and public involvement

None.

RESULTS

Smoking prevalence rates varied widely across the countries and regions represented in EAGLES (Table 3). Smoking rates were highest in the Russian Federation and Eastern Europe. Australia, Brazil, Canada, and Mexico had smoking prevalence rates below 15%. There was also marked variability in countries' GDP, with Denmark and Australia registering as the highest income countries, and South Africa and Bulgaria as the lowest among EAGLES countries. Relative cost of cigarettes was highest in South Africa and Bulgaria; the United States had the

lowest cigarette RIP in 2014. MPOWER scores ranged from a low of 14 in South Africa to a high of 34 in Brazil. These four variables were not significantly correlated (data not shown).

Mean tobacco smoking prevalence was highest in Eastern Europe (32.8%) and tied for lowest in Australasia and North America II (Mexico) (15.0%). Although North America II (Mexico) had the lowest proportion of participants with psychiatric diagnosis and no active substance use disorders, participants enrolled in this country had the highest baseline levels of anxiety (5.8 ± 4.1), depression (3.7 ± 3.2), and aggression (62.2± 17.8) scores. South Africa had the lowest GDP *per capita* (6433 ± 0.0) and lowest MPOWER policy score (14.0 ± 0.0). South America had the highest MPOWER score (32.8 ± 1.1).

Table 3 Baseline characteristics by region (demographic, smoking, psychiatric, and country-level variables)

Variable		All (N=8144)	North America I (n=4539)	North America II (n=188)	South America (n=371)	Eastern Europe (n=818)	Western Europe (n=1750)	Africa (n=296)	Australasia (n=182)
Demographic characteristics									
Age, years, mean (SD)		46.5 (12.3)	46.5 (12.4)	47.6 (11.7)	51.7 (11.2)	42.9 (11.8)	48.1 (11.5)	41.3 (13.7)	43.2 (13.8)
Race	White	6649 (81.6)	3304 (72.8)	184 (97.9)	368 (99.2)	818 (100)	1736 (99.2)	116 (39.2)	123 (67.6)
	Black	1162 (14.2)	1071 (23.6)	1 (0.5)	2 (0.5)	0 (0)	2 (0.1)	86 (29.1)	0 (0)
	Other	332 (4.1)	163 (3.6)	3 (1.6)	1 (0.3)	0 (0)	12 (0.7)	94 (31.8)	59 (32.4)
Gender	Male	3592 (44.1)	1907 (42.0)	93 (49.5)	169 (45.6)	394 (48.2)	790 (45.1)	166 (56.1)	73 (40.1)
	Female	4552 (55.9)	2632 (58.0)	95 (50.5)	202 (54.4)	424 (51.8)	960 (54.9)	130 (43.9)	109 (59.9)
Smoking characteristics									
FTCD score, mean (SD)		5.8 (2.0)	5.7 (1.9)	5.5 (2.1)	5.5 (2.3)	6.2 (2.1)	5.8 (2.0)	5.1 (1.9)	5.5 (2.0)
Cigarettes per day in past month, mean (SD)		20.7 (8.2)	19.5 (7.7)	19.5 (7.7)	26.6 (11.4)	23.1 (8.1)	21.7 (7.9)	19.1 (9.2)	18.9 (7.0)
Living with smoker		2931 (36.0)	1655 (36.5)	69 (36.7)	134 (36.1)	398 (48.7)	486 (27.8)	125 (42.2)	64 (35.2)
Prior treatment	Prior varenicline use	1271 (15.6)	934 (20.6)	7 (3.7)	10 (2.7)	1 (0.1)	236 (13.5)	18 (6.1)	65 (35.7)
	Prior bupropion use	844 (10.4)	640 (14.1)	1 (0.5)	17 (4.6)	0 (0)	127 (7.3)	39 (13.2)	20 (11.0)
	Prior NRT use	2136 (26.2)	1551 (34.2)	9 (4.8)	3 (0.8)	27 (3.3)	450 (25.7)	20 (6.8)	76 (41.8)
Psychiatric characteristics									
Comorbid psychiatric diagnosis		1511 (18.6)	1092 (24.1)	2 (1.1)	42 (11.3)	13 (1.6)	282 (16.1)	31 (10.5)	49 (26.9)
No primary mood disorder		4028 (49.5)	2037 (44.9)	134 (71.3)	243 (65.5)	446 (54.5)	843 (48.2)	225 (76.0)	100 (54.9)
Primary mood disorder		2910 (35.7)	1883 (41.5)	44 (23.4)	50 (13.5)	138 (16.9)	691 (39.5)	56 (18.9)	48 (26.4)
Primary anxiety disorder		792 (9.7)	424 (9.3)	6 (3.2)	69 (18.6)	110 (13.4)	156 (8.9)	4 (1.4)	23 (12.6)

Variable	All (N=8144)	North America I (n=4539)	North America II (n=188)	South America (n=371)	Eastern Europe (n=818)	Western Europe (n=1750)	Africa (n=296)	Australasia (n=182)
Primary psychotic disorder	390 (4.8)	193 (4.3)	2 (1.1)	4 (1.1)	121 (14.8)	49 (2.8)	10 (3.4)	11 (6.0)
Borderline personality disorder	24 (0.3)	2 (<0.1)	2 (1.1)	5 (1.3)	3 (0.4)	11 (0.6)	1 (0.3)	0 (0)
HADS anxiety score, mean (SD)	4.0 (3.6)	4.2 (3.6)	5.8 (4.1)	3.4 (2.9)	2.2 (2.7)	4.2 (3.5)	3.7 (3.7)	4.6 (3.5)
HADS depression score, mean (SD)	2.4 (2.9)	2.4 (2.9)	3.7 (3.2)	2.1 (2.5)	2.0 (2.6)	2.4 (3.1)	2.2 (2.5)	2.3 (2.8)
Aggression Q total score, mean (SD)	55.5 (17.4)	54.5 (18.2)	62.2 (17.8)	62.2 (17.1)	55.2 (15.7)	55.5 (15.7)	57.3 (17.2)	56.6 (17.0)
C-SSRS BEID	1623 (19.9)	1010 (22.3)	37 (19.7)	25 (6.7)	14 (1.7)	430 (24.6)	97 (33.5)	67 (36.8)
Alcohol/substance dependence/use	957 (11.8)	778 (17.1)	0 (0)	12 (3.2)	5 (0.6)	109 (6.2)	33 (11.7)	36 (19.8)
Any psychotropic medication use	2325 (28.5)	1459 (32.1)	22 (11.7)	80 (21.6)	294 (35.9)	377 (21.5)	51 (17.2)	42 (23.1)
Newly derived country-specific variables								
Tobacco prevalence, mean (SD)	22.9 (4.6)	21.5 (1.9)	15.0 (0.0)	22.3 (3.9)	32.8 (2.8)	24.1 (3.7)	20.0 (0.0)	15.0 (0.0)
GDP, mean (SD)	43 972.4 (17 700.4)	54 792.6 (998.1)	10 922.0 (0.0)	12 429.5 (494.5)	11 498.7 (4651.8)	47 028.9 (7833.6)	3433.0 (0.0)	50 177.2 (8351.7)
Cigarette RIP, mean (SD)	1.7 (1.0)	1.1 (0.1)	3.1 (0.0)	1.5 (0.2)	3.1 (1.2)	1.6 (0.3)	3.5 (0.0)	3.0 (0.3)
MPOWER score, mean (SD)	24.3 (4.2)	22.6 (2.4)	26.0 (0.0)	32.8 (1.1)	28.4 (1.4)	25.9 (3.1)	24.0 (0.0)	29.3 (1.9)

All data are given as n (%) unless otherwise specified.

BEID, behavior and/or ideation; C-SSRS, Columbia–Suicide Severity Rating Scale; FTCD, Framework Convention on Tobacco Control; GDP, gross domestic product; HADS, Hospital Anxiety and Depression Scale; NRT, nicotine replacement therapy; Q, questionnaire; RIP, relative income price; SD, standard deviation.

Seven-day end-of-treatment PPA varied widely across regions (Figure 1), with the lowest rates found in Australasia (22.0%) and North America I (22.5%) and the highest rate (55.9%) in North America II (Mexico).

Table 4 depicts the results of the stepwise regression model examining the association of the 17 candidate predictor variables and the primary endpoint of 7-day PPA. Consistent with prior analyses of EAGLES data, individuals of Black compared to White race (OR 0.622 [95% CI 0.518, 0.748]), with psychotic disorders (0.605 [0.435, 0.841]), psychiatric medication use (0.789 [0.688, 0.904]), more cigarettes per day (0.968 [0.960, 0.976]) and contact with a smoker (0.856 [0.764, 0.961]) had lower odds of achieving short-term abstinence. Higher abstinence rates were observed in older participants (OR 1.010 [95% CI 1.005, 1.014]), with greater BMI (1.013 [1.004, 1.022]) and with prior varenicline use (1.228 [1.060, 1.422]). Additionally, all treatment groups demonstrated higher odds of abstinence as compared to placebo, as follows: varenicline (OR 3.808 [95% CI 3.260, 4.447]), bupropion (2.059 [1.755, 2.417]) and NRT (2.103 [1.793, 2.468]).

Table 4 Main-effect odds ratios for final stepwise logistic regression model of 7-day PPA, week 12

Effect*		Odds ratio estimate	95% lower CI	95% upper CI
Demographics	Age	1.010	1.005	1.014
	BMI	1.013	1.004	1.022
	Black race (vs White)	0.622	0.518	0.748
Psychiatric characteristics	Psychotic disorder	0.605	0.435	0.841
	Use of psychiatric medications	0.789	0.688	0.904
Smoking characteristics	FTND	0.907	0.879	0.936
	Cigarettes per day	0.968	0.960	0.976
	Contact with smoker	0.856	0.764	0.961
	Prior varenicline	1.228	1.060	1.422
Treatment group (vs placebo)	Varenicline	3.808	3.260	4.447
	Bupropion	2.059	1.755	2.417
	NRT	2.103	1.793	2.468

Region (vs North America I)	Eastern Europe	0.390	0.222	0.686
	South America	0.170	0.083	0.348
	Western Europe	1.356	1.140	1.613
Country-level variables	GDP†	0.544	0.468	0.631
	Cigarette RIP	0.617	0.528	0.722
	MPOWER	1.031	1.008	1.055

BMI, body mass index; CL, confidence interval; FTND, Fagerström Test for Nicotine Dependence; GDP, gross domestic product; NRT, nicotine replacement therapy; PPA, point prevalence abstinence; RIP, relative income price.

* Only most significant effects shown.

† GDP *per capita* per $10,000 USD.

After controlling for those traditional predictor variables, region remained in the model as a significant main effect. Using North America I (United States and Canada) as the referent, odds of achieving short-term abstinence were significantly higher in the Western European (OR 1.356 [95% CI 1.140, 1.613]) and lower in the Eastern European (0.390 [0.222, 0.686]) and South American (0.170 [0.083, 0.348]) regions.

Of the four country-level variables, three predicted abstinence (Table 4). Lower odds of abstinence were seen with higher GDP (OR 0.544 [95% CI 0.468, 0.631]) and higher cigarette RIP (0.617 [0.528, 0.722]), whereas higher odds were seen with higher MPOWER score (1.031 [1.008, 1.055]). Notably, tobacco smoking prevalence was not included in the model.

DISCUSSION

As predicted, individual-level variables of demographic, psychiatric, and smoking-related characteristics, as well as country-level variables of income, cigarette relative income price, and implementation of tobacco control policy, were associated with the likelihood of quitting. Specifically, the higher the income of a country and the more expensive cigarettes relative to a country's per capita GDP, the lower the likelihood of abstinence at end of treatment. Conversely, more stringent tobacco control policy implementation was associated with increased rates of

abstinence. Finally, country-level tobacco prevalence at the time the EAGLES study was conducted was not significantly correlated with abstinence initiation rates. After controlling for these and other traditional predictor variables, global region was still found to be a significant independent predictor of short-term smoking abstinence.

Despite adhering to the same study protocol with standardized inclusion and exclusion criteria used to enroll smoking participants, baseline characteristics by region differed broadly across the board with respect to age, gender, race, psychiatric history, psychiatric symptoms, prior treatments, severity of tobacco use and dependence, and substance use history. For instance, participants enrolled in the South American region were the oldest, smoked the most cigarettes per day, and were 99% White; Africa was the only region where males predominated and participants were predominantly non-White. Some regions had a substantial number of participants who had previously tried smoking cessation treatments, but regions such as Eastern Europe and North America II (Mexico) had hardly any. These individual-level characteristics have been shown to be independently associated with tobacco cessation outcomes, both in our earlier analysis [18] and in the literature more generally [13, 23, 28]. There is a growing body of literature suggesting the benefit of interventions specific to these risk factors [29-31], and one might extrapolate a potential benefit in tailoring a region's tobacco control plan to its unique characteristic makeup.

We found that a greater degree of tobacco control policy implementation, as reflected by higher MPOWER scores, was associated with higher odds of achieving short-term abstinence in EAGLES. This suggests that greater tobacco regulation is associated with higher quit rates, which is corroborated by the literature [32] and aligns with the greater mission of the FCTC. Although it may be presumed that greater tobacco control would be found in higher-income

regions and reflected by higher-priced and taxed cigarettes, our analysis did not find that to be the case. In fact, not only did we *not* find a correlation between those variables, but we found an inverse relationship with cessation rates. Our analysis found that higher income and more expensive cigarettes (i.e., higher RIP) were associated with lower cessation rates. This paradox comes as a surprise among the growing body of literature reporting that higher-income countries have had more drastic reductions in smoking prevalence [5], thought to be due to greater funding for and access to cessation interventions [33]. However, a newer, large-scale global analysis, published by Sathish *et al* [34], found that smokers in high-income countries were consuming cigarettes with much higher levels of nicotine than those in middle- or lower-income countries, which might make it harder to quit [34]. The literature also supports the idea that increasing the price of cigarettes is associated with a greater likelihood of quitting [6, 35], which is in opposition to our finding. But here again, as demonstrated in South Africa [36], raising prices on cigarettes via taxes may inadvertently lead to a proliferation of illicit cigarettes and the introduction of cheaper local brands, which may undermine tobacco regulatory efforts.

One possible explanation for these curious results is the controversial "hardening hypothesis" that smokers who find it easier to quit have already done so, leaving "hardened" smokers. If someone continues to smoke cigarettes despite the increasing cost, that individual may fall under the umbrella of a "hardened" smoker, and thus have more difficulty quitting. The same may apply to higher-income regions, with presumed greater access to healthcare and cessation resources. However, hardening is commonly attributed to populations with lower smoking prevalence [14-16], and in our analysis, a region's smoking prevalence rate at the time EAGLES was conducted was not a significant predictor of smoking cessation success once other variables were included in the model. Basing the hardening hypothesis purely on smoking

prevalence at a single time point is likely too reductionist a model. For example, Cheung *et al* found a model that may unite contradictory findings about hardening [37]. Their sample showed a U-shaped relationship between the odds of quitting smoking and smoking prevalence, in which odds of quitting were highest at either extreme of the smoking prevalence curve.

Even though we examined these regional effects in a more granular, seven-region context compared with our prior EAGLES analyses, which considered only a US/non-US dichotomy, the region from which subjects were enrolled remained a significant main effect in the analytic model despite also controlling for treatment group and psychiatric subcohort. The EAGLES dataset was not intended to represent the global population of smokers at large, nor was its enrollment strategy designed to randomize participants within each of the countries participating. Nevertheless, our regional findings appeared to have similar trends to others described in the literature. Our prior work [13] did not make the distinction between Eastern and Western Europe, but found that European smokers had higher rates of abstinence overall compared with US smokers. In our current analysis, we found that, when compared to North American I (United States and Canada) participants, smokers enrolled in the Western European region had approximately one-third higher odds of abstinence, whereas enrollees in Eastern Europe had less than half the odds of quitting. The literature supports this finding, and when compared to Western Europe, Eastern Europe has been found to have lower smoking cessation rates [38], higher smoking prevalence rates, and higher rates of morbidity and mortality attributable to tobacco [5]. These challenges are thought to be due to more accessible cigarettes, less tobacco control, and particular cultural and religious practices in the region [5]. We also found that smokers enrolled at sites in South America had the lowest odds of successful cessation – about one-quarter of the odds in North America I (Table 4). A 2008 review paper from Muller and

Wehbe [39] examined unique factors in Latin America that contribute to its growing tobacco epidemic, particularly that this region includes some of the highest tobacco-producing countries in the world (in our dataset, Brazil #3 and Argentina #9), and that such an economic reliance on tobacco products has likely contributed to less rigorous tobacco control, less expensive cigarettes, and an ongoing tobacco smuggling trade [39]. It is curious then, in our analysis, that this region had the *highest* MPOWER score. Because our model was designed to include all regions, each predictor might not extrapolate to each individual region.

Our analyses were not without limitations. The EAGLES trial was not designed to recruit representative samples of a country's smokers, but rather, to enroll smokers who met prespecified inclusion/exclusion criteria into a methodologically sound, randomized controlled trial comparing the first-line smoking cessation medications and placebo. Thus, the results might not generalize to the global population of smokers at large and may not be representative of each country's smokers. Sites enrolling participants in EAGLES were located primarily in high- and upper-middle income countries, further limiting generalizability. Over half the EAGLES participants were enrolled in the United States, an imbalance that could have affected results. Although we controlled for treatment condition and psychiatric cohort in our analyses and examined correlations among the newly introduced country-level variables, we cannot rule out multicollinearity among predictor variables affecting the results. Moreover, we did not assess how sociocultural factors, including differences in stigma levels surrounding reporting mental health conditions across countries, may have influenced results. Nonetheless, EAGLES remains the largest, most rigorous, placebo-controlled, multinational trial of smoking cessation medications ever conducted, and the new results obtained will help inform subsequent analyses in samples more representative of smokers across the globe.

In conclusion, geographic region had a significant effect on the odds of achieving short-term smoking abstinence in EAGLES even after controlling for treatment, psychiatric comorbidity, individual-level, and country-specific variables. Increased tobacco control policy and enforcement was associated with greater chance of achieving short-term abstinence, which supports the argument that tighter regulation is associated with enhanced efficacy of smoking cessation treatments. Although seemingly contradictory, increased income of a country and more expensive cigarettes were associated with lower odds of abstinence, which might reflect hardening of smokers in those countries. The literature remains mixed about whether hardening truly exists; it may be that a deeper understanding of this complex phenomenon is needed, rather than refuting the validity of the hypothesis itself.

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Contributors AEE and RMA were involved in the conception and design of the parent study; BD, DEL, BSM, PS, TM, AEE and RMA were involved with the *post-hoc* analyses and/or interpretation of the data. DEL performed the statistical analyses. RMA and DEL are responsible for the overall content as guarantor. All authors were involved in the drafting of the manuscript and revising it critically for intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Patient consent for publication All patients provided written, informed consent and were reimbursed for study participation time and travel expenses as determined by each trial site.

Ethics approval EAGLES was reviewed and approved by each site's institutional review board or ethics committee and was conducted in accordance with the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines.

Data availability statement Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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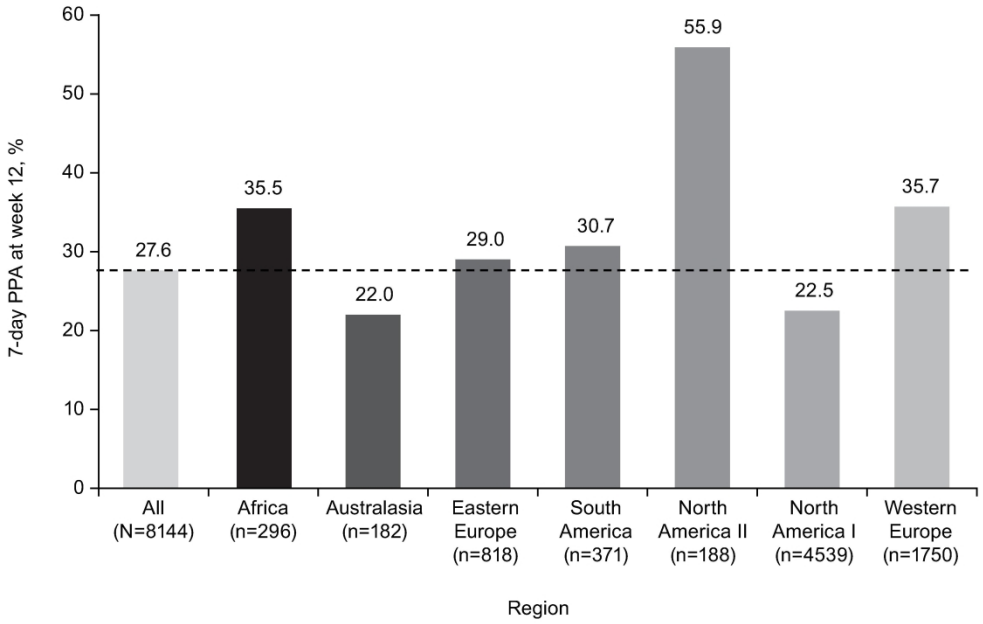
<FIGURE LEGEND>

Figure 1 Seven-day PPA at week 12 by region. All patients randomized. PPA, point prevalence abstinence.



Seven-day PPA at week 12 by region. All patients randomized. PPA, point prevalence abstinence.

180x118mm (600 x 600 DPI)

Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORTreporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	3
Introduction			

Background and objectives	#2a	Scientific background and explanation of rationale	5-6
Background and objectives	#2b	Specific objectives or hypothesis	7-8
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	8*
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	8*
Participants	#4a	Eligibility criteria for participants	8-9
Participants	#4b	Settings and locations where the data were collected	7-8*
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8*
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	9-10
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	8*
Sample size	#7a	How sample size was determined.	8*

Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	8*
			8*
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size) - 8*	
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8*
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	8*
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	8*
Blinding	#11b	If relevant, description of the similarity of interventions	8*
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	11-12

Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11-12
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8*
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	8*
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	8*
Recruitment	#14b	Why the trial ended or was stopped	8*
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	14-15
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8*
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16-17
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	15-16

Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8*
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	8*
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	21
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	21
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-20
Registration	#23	Registration number and name of trial registry	8
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19-20
Registration	#23	Registration number and name of trial registry	8
Protocol	#24	Where the full trial protocol can be accessed, if available	8*
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	23

*Referenced in the paper but more explicitly elaborated in primary outcome paper (Anthenelli RM, Benowitz NL, West R, *et al.* Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;387:2507-20)