Trends in the heritability of smoking*

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Abstract

We describe trends in the genetic influences on regular smoking across multiple cohorts of U.S. adults born between 1920 and 1970. Using a sample of 348 identical twin pairs and 321 same-sex fraternal twin pairs from the National Survey of Midlife Development in the United States, we estimate the heritability for regular smoking to be 42 percent. Using a rolling sample we show that the timing of the first Surgeon General's Report coincides with an increasing influence of genetic factors on the likelihood of regular smoking, but subsequent legislation prohibiting smoking caused a significant reduction in the genetic causes for regular smoking. We argue that genetic associations for smoking should be conceptualized within and across broad social-historical trends. Systematic variation in the genetic influences across periods makes it difficult to estimate genetic effects on health behaviors from data obtained from a single point in time. Without properly describing the location of the sample within the larger epidemiological trend, the results from genetic studies are difficult to interpret and may lead to erroneous conclusions about the genetic factors that may underlie complex behaviors like smoking.

Introduction

In this paper we use a nationally representative sample of same-sex adult twin pairs born between 1920 and 1970 to model variation in the heritability of regular smoking across fifty years. We argue that genetic influences on smoking are part of a dynamic system that changes and evolves over time. We further argue that these changes are not random, and we illustrate this point by examining the heritability of smoking before and after the Surgeon General's Report in 1964. This single event allows us to test several hypotheses regarding the causes of cigarette smoking and illustrates the importance of considering the historical context of genetic studies.

Gene-environment interplay and smoking

Based on studies that compare the concordance of smoking among identical twin pairs to that of fraternal twin pairs, researchers estimate that roughly 50 to 60 percent of the variance of regular smoking is due to genetic factors (1-4). However, as Kendler et al. (5) highlight, these estimates are subject to change over time. These researchers compare reported tobacco use among same-sex twin pairs across three birth cohorts (1910-1924, 1925-1939, and 1940-1958). Among the first cohort of women, none of the variance in tobacco use was due to genetic factors but by the third cohort, the heritability for regular tobacco use was nearly 60%. These results are consistent with the *social control* gene-environment interaction (GxE) model (6) which posits that "norms and other social forces that 'canalize' (i.e., restrict variability in the phenotype of) genetically diverse people. As these canalization forces increase (i.e., norms are more effective and choices are minimal), genetic differences are of diminishing consequence." (6:69). The same understanding is applicable to studies showing that genetic influences on the use of tobacco use and

alcohol are either muted or non-existent among those who are raised with a strong religious upbringing with clear norms against the use of different substances (7, 8).

The social control model assumes that there are shared behavioral expectations and corresponding sanctions that influence genetic associations. In other words, the social environment *causes* genes to operate differently. However, it is also possible that the contribution of genetic factors to overall variance of a behavior will vary across social contexts but the environment is *not causing* the genes to operate differently. Instead, the environment simply clarifies or obscures the role of genes. If the composition of smokers changes because more people (regardless of genetic makeup) begin smoking, then there will be a point in the distribution of smoking environments that entrée into smoking is primarily a socially oriented phenomenon; genetically vulnerable persons are no more likely to begin smoking than genetically resilient persons simply because dominance of the social processes related to smoking. This process can be characterized by a tipping point in which, prior to this point time, there are *active* social forces that are shaping the understandings and expectations of smoking; however, at some point after norms have been established, smoking prevalence becomes the dominant causal factor and, despite the fact that genotypes may differentiate individuals from one another, the contribution of genes is relatively less important. As a result, in socially dominant contexts, the heritability of smoking will decrease in salience.

Alternatively, it is also possible that changes in the social norms regarding smoking will lead to an *increase* in the relevance of genetic factors. Raine (9) calls this the "social push perspective" and suggests that we should examine genetic associations in *benign* environments or those that lack social factors that encourage smoking. Under this

perspective, if an individual with genetic tendencies to smoke cigarettes lacks social factors that "push" them to smoke, then biological factors may better explain their smoking. As Raine makes clear, this perspective does not mean that the environment causes genes to operate differently, rather it simply minimizes the "noise" in the study which allows for "biology to shine through" (9: p. 14).

Smoking Trends and the Surgeon General's Report

National trends in cigarette consumption are presented in Figure 1. Cigarette consumption increased more than five-fold from 1920 to 1960, reached a plateau between 1965 and 1975, and has declined consistently since this time. By some estimates, roughly one-half of men and one-third of women in the United States smoked regularly in 1966 (10). Two important changes took place during the 1960s and 1970s that had important implications for smoking. The first event occurred in 1964 when the Surgeon General released the first of a number of reports with clear warnings about the dangers of smoking. This led to the *Federal Cigarette Labeling and Advertising Act* which required the Surgeon General's Warning on all cigarette packages that read: "Caution: Cigarette Smoking May Be Hazardous to Your Health." The first report focused on the link between smoking and lung cancer and was followed by a series of reports linking smoking to heart disease (11) and low birth weight (12) and making a case for the risks of second hand smoke for vulnerable populations (13). These efforts led to the 1971 Public Health Cigarette Smoking Act which banned the advertising of cigarettes on both television and radio.

The second series of events occurred in the mid 1970s. In 1973, Arizona passed a comprehensive law that limited smoking in public places which was the first effort to formally control public smoking behaviors. This was followed by a more restrictive set of laws including the 1975 Minnesota Clean Indoor Air Act which required restaurants to have non-smoking sections in their restaurants; another twelve years would pass until Aspen, CO became the first city to formally ban all cigarette smoking in restaurants. The push for bans in all restaurants was bolstered by the 19th Surgeon General's Report, which argued that the "simple separation of smokers and nonsmokers within the same airspace may reduce but cannot eliminate nonsmoker exposure to environmental tobacco smoke." (14)

The time-lag between scientific findings about the health risks of smoking and legislation designed to limit smoking is important because the former may influence the social component of smoking behaviors but the later may be particularly effective in influencing the genetic component of smoking. That is, norms about smoking were starting to change in the 1960s because of the shared understanding of regarding the health risks of cigarette smoking, but it wasn't until the 1970s, in which institutional controls were formalized, that the environment had a causal influence on genetic influences.

This historical backdrop provides an unusual opportunity to examine both causal and non-causal GxE and the timing of the first Surgeon General's Report serves as an experimental design to test the relevance of considering the smoking population as a socio-genetic composition which changes over time. Using the causal/non-causal GxE

distinction in combination with the changing social and institutional forces with respect to smoking, we hypothesize that genetic influences on smoking will change as follows:

- Period 1 (prior to 1964): This period was characterized by the low cost and ubiquitous availability of cigarettes in conjunction with regular images of cultural icons smoking. The socio-genetic composition of smokers is dominated by social entrée into smoking and during this period, *the heritability of smoking will decrease*.
- Period 2 (1965-1975): During this period, the clear evidence provided by the scientific community lead many to stop smoking. This change should be the least evident among those for whom smoking is genetically oriented and *the heritability of smoking will increase.*
- Period 3 (1975-1995): Local, state, and federal lawmakers enact and enforce policies aimed to reduced cigarette consumption. These social controls will causally influence the degree to which genetic characteristics differentiate between individuals. Thus, during this period, *the heritability of smoking will decrease*.

METHODS

Data

This study uses data from the 1995 National Survey of Midlife Development in the United States (MIDUS) (15). MIDUS is a nationally representative survey designed to study the effects of midlife development on the self-reported physical health, psychological well-being, and social consciousness of adults aged 25 to 75. Data in the survey were collected through the use of a telephone interview and a mailed questionnaire to nearly 7,000 respondents. The MIDUS Twin Screening Project was used

to identify 998 adult twin pairs to participate in the study. After a screening of roughly 50,000 households via a telephone interview, MIDUS interviewers contacted the respondent who was then asked to contact their twin to participate in the study. Of the 998 pairs, 1914 individuals completed at least some portion of the telephone survey with an overall response rate 96%. We use only same-sex monozygotic (MZ) and dizygotic (DZ); dropping twins whose co-twins did not participate in the survey, we have 350 pairs of MZ twins and 322 pairs of same-sex DZ twins. Questions used in this study come from the telephone interview and the extent of missing data is minimal. Of these, one pair of MZ twins was dropped due to missing smoking data and two pairs were dropped due to differing birth dates. The remaining sample used in the study included 348 MZ pairs and 321 same-sex DZ pairs.[1]

Regular smoking was assessed through two questions. Respondents were asked, "Have you ever smoked cigarettes regularly - that is, at least a few cigarettes every day?" Those responding "yes" were then asked, "On average, about how many cigarettes did you smoke per day during the one year in your life when you smoked most heavily?" Respondents indicating that they smoked less than three cigarettes per day during the time of heaviest smoking were considered to have never been a regular smoker. Respondents indicating that they have smoked regularly were also asked "At what age did you begin smoking regularly?"

To establish the heritability of smoking we use survival models with shared frailty among twin pairs. This model is specified in equation 1. The values for T are random variables capturing the survival times (the age of onset for regular smoking) for the jth sibling in the ith pair of twins. Thus, the survival function is conditional on this cluster-

specific error term *Wi,* and the resulting hazard functions $h(t_{ij} \mid w_i)$ are multiplicative frailty models with a baseline hazard $\lambda_0(t_0)$.

$$h(t_{ij} \mid w_i) = w_i \lambda_0(t_{ij}) \exp\{(\beta(t_{ij})' x_{ij}(t_{ij})\} \quad (1)$$

Our model assumes that *Wi* has a gamma distribution indexed by α with the following density: $f(w_i) = w_i^{\alpha-1} e^{-\alpha W_i} \alpha^{\alpha} / \Gamma(\alpha)$. The distributional parameters for this density are mean = 1 and a variance of φ. The latent random effects of φ are assumed to affect the hazard multiplicatively. This model is particularly useful for our purposes because the ratio of φ/(2+ φ) is equivalent to Kendall's (16) coefficient of intra-cluster rank correlation (see Guo and Rodriguez, 1992 for a detailed discussion). Thus, by estimating φ for MZ pairs and DZ pairs separately, pairwise correlation coefficients can be calculated that take into account the duration of exposure and the subsequent onset of regular smoking. We estimate the heritability of regular smoking as twice the difference of the correlations between MZ and DZ pairs. Results for the full sample models are in Table 2.

To address our primary research question, we then estimate similar models by the year of birth of the sibling pairs. This provides a trend for the heritability of smoking for those born in the 1920s through the 1960s. Because of small sample sizes for each birth year in our study, time specific heritabilities are calculated for a rolling sample with a window of 4 years. For example, an estimate for 1925 includes individuals born in 1925 and those born within the four years before and after 1925. We do this for each year between 1920 and 1970. These models also include controls for gender and the equal environments assumption.[2]

Results

Table 1 presents information on the number of twin pairs by decade of birth. Nearly 90% of the MZ pairs were concordant for smoking status in the 1920s compared to 66% among DZ pairs during this same time; these estimates provide somewhat crude evidence for the genetic influence on smoking. However, it is also clear in this table that the concordance for MZ and DZ pairs changes over time. That is, while the concordance of DZ pairs did not change for the first two decades, the concordance among MZ pairs fell appreciably and by the third decade, there is little difference in the concordance between MZ and DZ pairs. Following a spike in the fourth decade, the excess concordance among MZ pairs is absent in the final cohort. From these simple numbers, it appears as though genetic influences on smoking are the lowest among those born in the 1940s and the 1960s and highest among those born in the 1920s and the 1950s. These initial findings are in line with the hypothesized associations described earlier.

[TABLE 1 ABOUT HERE]

To provide a more detailed assessment of this association which models the timing of regular smoking while also taking into account individuals who never smoked regularly (right censored) and controls for gender and the equal environments measure, survival models are estimated separately for MZ and same-sex DZ pairs. These results are presented in Table 2. For the full sample (results shown at the bottom of Table 2) the hazard function is significantly improved when the shared frailty among pairs is considered for both MZ ($\chi^2 = 110.79$, $p<.001$) and DZ ($\chi^2 = 40.54$, $p<.001$) pairs. This estimate ($\varphi_{mz} = 2.73$) for MZ pairs is more than twice that of DZ pairs ($\varphi_{dz} = 1.15$) and it provides a pairwise correlation of .58 and .37 for MZ and DZ pairs, respectively. Using

twice the difference of these estimates as a rough indication of heritability, these estimates suggest that genes account for roughly 42% of the variance in the timing of regular smoking among adults.

[TABLE 2 ABOUT HERE]

To address the primary aim of this study, this same model was repeated 43 times spanning the birth years of 1924 to 1964. The first column presents the observed number of pairs for each year of birth and the second column describes the number of pairs that were used in the rolling sample to estimate the intra-pair correlation for that year. The shared frailty variance estimate and the significance of this estimate as well as the corresponding pair-wise correlation coefficient are also provided. The final column provides the yearly estimate of the heritability of regular smoking. This final column is presented graphically in Figure 2.

The primary contribution of this paper is summarized by the results presented in Figure 2. That is, although the heritability estimate calculate in Table 2 ($h^2 = .42$) summarizes the entire sample, this estimate should be understood as an average; at times genetic influences are much higher and much lower than this value. The heritability of regular smoking appears to be the most pronounced among those born in the early 1920s and for those born in the mid 1950s. The first minimum in this figure (1945) corresponds with the hypothesized transition between the social and genetic composition of smokers following the Surgeon General's Report. That is, those born between 1944 and 1945 are at the peak of their smoking risk roughly 20 years later when the 1st report was released. Because these estimates are related to year of birth, Figure 1 presents the heritability estimates adjusted by 21 years (the peak of smoking onset). According to this estimate,

genetic factors only accounted for eight percent of the variance in regular smoking during this transitional period.

However, following this first transition there is a persistent and steady increase in the genetic influences on regular smoking until the early 1970s. We argue that this increase captures a non-causal form of gene-environment interactions where the socio-genetic composition of smokers is changing over time; primarily social smokers are the first to give up their smoking status in light of the evidence about the health risks. This perspective is in line with results showing that smoking desistence is the most highly heritable smoking phenotype (18). That is, those who have the hardest time quitting, may also be those who have a stronger physiologic dependence on nicotine and thus non-dependent individuals, once removed from the smoking population, cause the genetic factors responsible for nicotine dependence to become relatively more important.

The first legislative efforts to limit or ban smoking in public places occurred during the end of this period. According to our hypotheses, the genetic contributions to regular smoking will decrease under non-causal social compositional changes *or* if there are social forces (normative, institutional, or both) that act on the behaviors of individuals as a source of control. As described earlier, this period extends until the early 1990s and is characterized by an increasing number of federal, state, and local laws that controlled the sale, distribution, advertisement, and smoking of tobacco. In other words, changes in the social orientation of smoking did not *causally* influence genetic factors related to smoking onset or persistence until laws were developed and enforced that placed physical limits on this behavior. These legislative efforts reflect the forces described by Shanahan and Hofer (6) that restrict the variation of genetic factors and the steep drop in the

heritability of regular smoking corresponds with the social control perspective of gene-environment interactions.

Discussion

The findings presented in this paper speak to an increasing body of work that quantifies genetic and environmental contributions to smoking in the population. As we have argued elsewhere, heritability estimates should be considered averages, and we should anticipate dispersion about this average. The context for this dispersion may be discrete social settings like schools (19) but, as we show here, it may also be a social historical trend. This point is made nicely by Rutter (20: p. 60, *emphasis added*) who argues that:

> There is not, and cannot be, any absolute value for the strength of genetic influences on a trait, no matter how accurately the trait is measures or how carefully the genetic effect is assessed. As behavioral genetics have long recognized, and emphasized, heritability figures are necessarily specific to populations and to *time periods*.

Despite the general acceptance of this perspective, little work has emphasized variation in heritability estimates over time. Our paper is one of few papers to use a nationally representative sample of twins to examine quantitative genetic estimates of regular smoking and the only known paper to show the trends in the heritability estimate across this important period in US history.

This perspective is particularly relevant in the recent push to find specific genes that predict smoking (21) because the effectiveness of methods to identify single-nucleotide polymorphisms across the entire human genome may be subject to periodic highs and lows in the genetic influences on a particular trait. The current methods certainly consider this factor (e.g., the population prevalence is a key component of the estimation techniques), but they do not necessarily consider that their sample is drawn from a specific historical moment in a larger cycle with predictable ebbs and flows. The

consideration of epidemiologic trends of cigarette use as causal and non-causal forms of gene-by-environment interactions in conjunction with quantitative genetic or genetic association methods to identify heritability forms a complicated picture of smoking. Out of this complexity, however, we argue that there may be relatively simple ways of considering which genetic and environmental effects change over time. Focusing on heritability estimates as part of a larger trend is particularly important to the study of epidemiology because it suggests that health-related policies should consider the timing of the policy implementation as a function of this larger trend.

NOTES

1. Date of birth was assumed for 29 individuals based on their co-twin's reported date of birth. 4 pairs reported different birth dates. Two of these pairs were dropped because their birth dates differed by several years – probably due to coding error. The other two pairs had birth dates differing by one year; for these twins, we used the earliest reported birth date. The date of birth for 8 pairs were imputed from their age (based on the oldest age reported) because both twins were missing a date of birth. In addition, because of the limited sample sizes and a failure of convergence at this time, we generated two pseudo observations of male DZ pairs for the year 1929. One pair was concordant for smoking and the other was discordant. The EEA values were given zero, the mean. There is no evidence that this insertion caused problems for this point in time.

2. Violations to the equal environments assumption, resulting from MZ twins being treated more similarly than DZ twins can increase concordance among MZ twins and overestimate heritability estimates. The MIDUS twin data includes three questions assessing how often twins were dressed alike, placed in the same classrooms, and had the same playmates. These measures have been used to gauge and correct EEA violations (22). We create a composite EEA score using a polychoric principle components analysis of the pair's mean response on the three items and include this estimate as a control in all models. We do not expect twin pairs who are treated more similarly to one another to be more likely to smoke, rather they will be more alike one another. Thus, if MZ pairs are like one another because they are more likely to share environments, then this control should reduce the frailty variance estimate for MZ pairs more so than DZ pairs.

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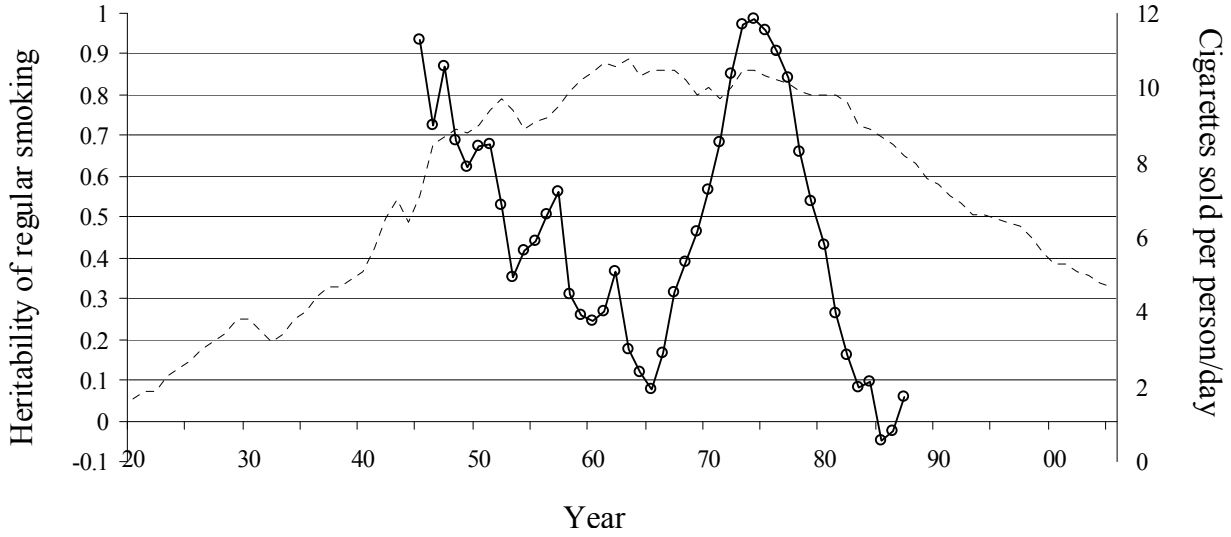
TABLE 1. Sample size, smoking prevalence, and concordance rates among pairs by birth year

	Monozygotic (identical) Twins			Dizygotic (fraternal) Twins		
Year of Birth	N (pairs)	% Smoke	Concordance	N (pairs)	% Smoke	Concordance
1920s	19	0.42	0.89	29	0.28	0.66
1930s	51	0.49	0.76	42	0.52	0.66
1940s	84	0.45	0.79	85	0.52	0.73
1950s	107	0.37	0.82	87	0.56	0.67
1960s	87	0.35	0.78	78	0.34	0.79

TABLE 2 Year specific heritability estimates for the onset of regular smoking

	MZ						DZ						
Year	N	Nm	φ	$\chi 2_{\varphi}$	p<	r	N	Nm	φ	$\chi 2_{\varphi}$	p<	r	h^2
24	2	19	1.76	4.21	0.02	0.47	5	22	0.00	0.00	0.50	0.00	0.94
25	1	19	1.76	4.21	0.02	0.47	1	30	0.24	0.12	0.36	0.11	0.72
26	5	22	3.10	8.11	0.00	0.61	5	33	0.42	0.45	0.25	0.17	0.87
27	2	25	2.47	8.81	0.00	0.55	2	34	0.53	0.93	0.17	0.21	0.69
28	3	26	1.94	7.87	0.00	0.49	1	36	0.44	0.82	0.18	0.18	0.62
29	0	27	1.51	6.59	0.01	0.43	9	34	0.21	0.23	0.32	0.09	0.67
30	4	31	1.84	7.67	0.00	0.48	4	35	0.32	0.62	0.22	0.14	0.68
31	4	36	1.29	6.23	0.01	0.39	5	33	0.29	0.56	0.23	0.13	0.53
32	5	37	1.24	5.53	0.01	0.38	4	35	0.52	1.89	0.08	0.21	0.35
33	3	45	1.40	8.89	0.00	0.41	3	37	0.51	1.79	0.09	0.20	0.42
34	5	47	1.50	10.42	0.00	0.43	2	34	0.52	1.68	0.10	0.21	0.44
35	10	47	1.53	10.40	0.00	0.43	3	38	0.44	1.59	0.10	0.18	0.51
36	3	47	1.25	7.53	0.00	0.38	4	37	0.23	0.49	0.24	0.10	0.56
37	11	46	1.21	7.12	0.00	0.38	3	44	0.57	2.53	0.06	0.22	0.31
38	2	49	1.39	8.57	0.00	0.41	6	48	0.78	4.64	0.02	0.28	0.26
39	4	51	1.27	9.66	0.00	0.39	8	57	0.72	4.51	0.02	0.27	0.24
40	4	50	1.53	9.66	0.00	0.43	4	61	0.85	6.20	0.01	0.30	0.27
41	4	53	1.98	13.38	0.00	0.50	11	68	0.92	6.73	0.00	0.31	0.36
42	6	52	1.57	11.22	0.00	0.44	7	75	1.08	9.43	0.00	0.35	0.18
43	7	61	1.65	13.80	0.00	0.45	11	74	1.29	11.96	0.00	0.39	0.12
44	9	72	1.64	15.66	0.00	0.45	7	73	1.40	12.77	0.00	0.41	0.08
45	6	80	2.04	23.71	0.00	0.50	11	81	1.46	16.55	0.00	0.42	0.16
46	10	89	2.18	27.94	0.00	0.52	10	80	1.15	12.21	0.00	0.36	0.31
47	11	86	2.43	30.00	0.00	0.55	5	76	1.09	10.28	0.00	0.35	0.39
48	15	87	3.02	34.01	0.00	0.60	7	70	1.17	11.06	0.00	0.37	0.46
49	12	90	3.90	48.27	0.00	0.66	12	71	1.22	10.90	0.00	0.38	0.57
50	13	97	3.41	46.38	0.00	0.63	10	71	0.81	6.65	0.00	0.29	0.68
51	3	95	3.62	43.99	0.00	0.64	3	75	0.56	4.63	0.02	0.22	0.85
52	8	102	4.10	48.23	0.00	0.67	5	78	0.46	3.55	0.03	0.19	0.97
53	12	95	4.65	50.44	0.00	0.70	8	80	0.52	4.16	0.02	0.21	0.98
54	13	94	3.99	40.04	0.00	0.67	11	75	0.46	3.00	0.04	0.19	0.96
55	8	94	4.66	41.32	0.00	0.70	14	77	0.66	5.19	0.01	0.25	0.91
56	18	102	4.42	47.17	0.00	0.69	8	85	0.73	6.97	0.00	0.27	0.84
57	8	100	3.93	41.55	0.00	0.66	9	89	0.99	10.47	0.00	0.33	0.66
58	11	98	3.34	33.18	0.00	0.63	7	96	1.11	13.03	0.00	0.36	0.54
59	13	97	3.67	33.58	0.00	0.65	12	92	1.52	18.29	0.00	0.43	0.43
60	11	94	3.02	26.13	0.00	0.60	11	84	1.77	18.84	0.00	0.47	0.26
61	6	81	2.52	19.39	0.00	0.56	9	80	1.83	18.21	0.00	0.48	0.16
62	10	82	2.49	20.21	0.00	0.56	15	76	2.12	21.08	0.00	0.51	0.08
63	12	79	2.68	19.75	0.00	0.57	7	74	2.21	18.73	0.00	0.52	0.10
64	5	75	2.25	15.72	0.00	0.53	6	71	2.48	16.90	0.00	0.55	-0.05
65	5	73	2.06	12.74	0.00	0.51	4	63	2.16	11.61	0.00	0.52	-0.02
66	9	70	2.35	14.56	0.00	0.54	5	58	2.10	9.70	0.00	0.51	0.06
Total	**348**	**-**	**2.73**	**110.79**	**0.00**	**0.58**	**321**	**-**	**1.15**	**40.54**	**0.00**	**0.37**	**0.42**

FIGURE 1. Trends in the sales of cigarettes (1920-2004) and the heritability of smoking (1945-1987) in the United States.



Note: Heritability estimates obtained from Table 2. Cigarette sales data obtained from Forey et al. (2007). The vertical (Y) axis describes the estimated proportion of variance in regular smoking that is due to genetic factors. The vertical (Z) axis describes the number of cigarettes sold in the United States per adult over the age of 15 per day.