Public Policy and the Genetics of Smoking

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Abstract

In this paper we explore the effect of historical and public policy changes in the genetic influences on smoking desistence. Using a sample of adult twins (n_{mz}=363, n_{dz}=233) from a large population registry, we estimate Cox proportional hazards models that describe similarity in the timing of smoking desistence among adult twin pairs and find that MZ twin pairs are significantly more likely to quit smoking in the same time frame, indentified by policy changes, compared to DZ twin pairs. The results provide strong support for the social push perspective for this phenotype. Specifically, we show that genetic factors for smoking desistence increase in importance following restrictive legislation on smoking behaviors that occurred in the early and mid 1970s. These findings make important contributions to the social demography and genetic epidemiology of smoking as well as the gene-environment interaction literatures.

Introduction

Environmental and genetic factors equally contribute to an individual's risk of becoming a regular smoker; heritability and environmental influence for regular smoking typically range between .4 and .6 (Carmelli et al. 1992; Sullivan and Kendler 1999; Hall, Madden, and Lynskey 2002; Li et al. 2003) and numerous candidate genes have been indentified (for a review see Munafo et al 2004). However, genetic influences on smoking vary considerably across different social environments (Boardman 2009; Boardman et al. 2008; Timberlake et al. 2006). Indeed, environmental moderation of genetic factors is anticipated by the gene-by-environment interaction (GxE) paradigm (Eaves, Silberg and Erkanli 2003; Shanahan and Hofer 2005) and there is relatively consistent evidence that environments may control or enable genetic tendencies to consume cigarettes. This is particularly true when the "environment" is characterized in broad historical periods, as social norms and institutional constraints unique to particular periods in time influence the degree to which genes differentiate between smokers and non-smokers (e.g., Kendler et al. 2000; Boardman, Blalock, and Pampel 2010).

Cigarette consumption increased more than fivefold from 1920 to 1960, reached a plateau between 1965 and 1975, and has declined consistently since that time. At the peak around 1966, roughly one-half of men and one-third of women in the United States smoked regularly (Forey et al. 2007). However, two changes took place during the 1960s and 1970s that had important implications for the genetics of smoking. First, the Surgeon General released the first of a number of reports with clear warnings about the dangers of smoking in 1964 which led to the Federal Cigarette Labeling and Advertising Act of 1965. This required that all cigarette packages contain a printed copy of the statement:

"Caution: Cigarette Smoking May Be Hazardous to Your Health." The second series of events began in the mid 1970s. In 1973, Arizona became the first state to formally control public smoking and pass a comprehensive law that limited smoking in public places. More restrictive sets of laws followed; including the 1975 Minnesota Clean Indoor Air Act, which required restaurants to have nonsmoking sections. Twelve years later 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 nineteenth Surgeon General's Report (USDHHS 1986), 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." By the end of 2007, the number of states requiring restaurants to be smoke-free increased to 21 and the number of states with no smoking restrictions for restaurants decreased from 19 to 9. The scientific community first declared that smoking was unequivocally hazards to one's health but it wasn't until the legislation of the 1970s, that clear restrictions were placed on individuals that limited their smoking behaviors. As others, have shown (Boardman et al. 2010), this context provides an interesting backdrop in which to study the genetics of smoking and it sheds light on the different gene-environment interaction models.

The current study extends this period-moderation perspective by examining smoking desistence as the phenotype. Researchers report heritability estimates of successful quitting to be in the range of .5 to .3 (Xian et al. 2003) but no existing work has focused on period effects on smoking desistence. Genes implicated in smoking onset are quite different from smoking desistence (Broms et al. 2006), and we suspect the period effects on the genetics of smoking desistence may be quite different as well.

Gene-environment interplay and smoking

There are two competing gene-environment interaction models regarding changing smoking policies and the genetics of smoking. The *social control* model hypothesizes that normative and institutional controls restrict the range of behaviors. As a result, two individuals within highly controlled environments may behave similarly but this has little to do with genetic similarity of the individuals; phenotypic similarity is simply a function of the social controls linked to laws and legal enforcement, moral codes, religious control, highly organized educational settings, or broad forms of stratification that limit particular individuals' mobility. For example, Timberlake et al. (2006) show that religious participation reduces the additive genetic influences on smoking onset among adolescents; their estimated 60% heritability nearly drops to zero for those who report that religion is "more important than anything else". Economic incentives are equally powerful; Boardman (2009) shows that states with higher excise taxes per pack of cigarettes, have the lowest observed heritability of regular smoking. Again, the taxes serve as an instrument of social control which ultimately dampens genetic influences.

Alternatively, the *social push* model (Raine 2002) hypothesizes that the public policies can actually highlight genetic influences by minimizing or maximizing "noise" that has the potential to overwhelm and hide the influences. According to this model, genetic associations are most clearly observable in benign environments that lack social factors encouraging genetically influenced addictive behaviors. When social noise is minimized, it allows for "biology to shine through" (Raine 2002:14). Conversely, when social factors "push" certain behaviors biological factors become harder to identify. Therefore, as social forces emerge that discourage smoking, or remove the positive

reinforcement for smoking, then the genetic influences on smoking may actually increase in salience because quitting may be much harder for those who have a genetic vulnerability to nicotine metabolism; over time those who are the most likely to be affected by the policy (those with little to know signs of nicotine addiction) are increasingly less likely to be in the smoking population.

Historical trends as "Environment"

The gene-environment perspective has been extended to include macro events measured by historical periods as structuring the genetics of smoking behaviors. Kendler et al. (2000) demonstrate that the heritability for tobacco use changes predictably over time. While estimates for men were relatively consistent across the three cohorts born between 1910-1924, 1925-1939, and 1940-1958 (h^2~.60), for women they showed that none of the variance in tobacco use was due to genetic factors in the first cohort but by the third cohort, there were no gender differences in the heritability estimates. They argue that women's smoking behaviors were highly controlled during the first cohort but absent these controls, genetic tendencies to use tobacco emerged. Boardman, Blalock, and Pampel (2010) estimate additive genetic influences for regular smoking among US adults born between 1920 and 1970 and show that the genetic influences on smoking reached a minimum (h^2 ~ .05) at the same time as the peak of smoking in the United States (roughly 1964). However, genetic influences on smoking increased sharply until the mid 1970s until declining again to levels reported by other studies. Boardman et al. (2010) argue that the first change (the minimum in 1964) was due to the first Surgeon General's Report regarding the dangers of smoking. That is, a non-causal social push mechanism was in

place in which genetic resilience facilitated a relatively quick departure from smoking for some, but genetic vulnerability made it more difficult for certain people to stop smoking and thus composition of smokers became more heavily influenced by genetic factors. This changed in the mid 1970s when the first legislation came on board that placed limits on the places in which people could smoke and increased taxes for cigarettes. These real controls, they argue, had a causal influence on the genetics of smoking at this time.

In this study, our goal is to extend the notion that historical trends may influence genetic influence, by examining a more specific smoking phenotype, smoking desistence. Previous studies focused on the onset of smoking and tobacco use (Boardman et al. 2010; Kendler et al. 2000).

However, no study has yet to explore macro level policy changes on the genetic influence on desistence the transition from regular smoker to non-smoker. We argue that smoking desistence denotes a stronger test of the social control vs. the social push model when the environment is characterized as a time period. If the social and institutional controls related to smoking desistence increased significantly starting in 1973, then the social control model would anticipate that the genetic influences on smoking desistence would *decrease* after this point. However, the social push model suggests that these forces would have a greater influence on the less genetically vulnerable, leaving the composition of smokers to be more influenced by genetic factors. Hence, following 1973, the genetic influences on smoking desistence should *increase*. The goal of this paper is to evaluate the relevance of these competing perspectives as related to this important behavior during this critical point in time.

Methods

Over 6,000 twin pairs were ascertained from a large population-based birth registry for the Commonwealth of Virginia, supplemented by twins recruited through a national mailer sent to the American Association of Retired Persons. Sample ascertainment and structure are described in detail by Truett et al. (1994) and Eaves et al. (1999). A large questionnaire on "Health and Life Styles" was first administered to the population in the late 1980s, which contained a broad set of items on health and clinical traits including the onset of regular smoking and the timing of smoking desistence. We only use twin pairs in which both members of the pair reported to have smoked daily at some point in their lives. Further, because of our emphasis on the1960s and 1970s we reduce our sample to twin pairs in which the first to quit did so between the years of 1960 and 1980. Meeting these criteria, our reduced sample consists of 363 MZ pairs and 233 same-sex DZ pairs from the larger study.

Study participants were asked about their lifetime smoking habits. Among those who responded that they smoked at least 1-5 cigarettes a day for some period of time, researchers asked "at what age did you start smoking?" They then asked "do you smoke now" and "if you have stopped smoking how old were you when you stopped?" These measures were used to calculate a pairwise measure indicating the length of time (in years) for a twin to quit smoking after his or her sibling has quit. Evidence for genetic influences on the cessation of smoking would be found by a reduced time to desistence among MZ twins compared to DZ twins.

The results presented in Table 1 are illustrative because they demonstrate a greater concordance among MZ compared to DZ desistence. However, this comparison is problematic because the measurement of desistence includes both observed values of

duration in which the co-twin stops and duration in which the desistence in unobserved and is thus right censored. This means that the measure of "quit within 2 years of one another" includes those who quit within 3 years of one another with those in which the co-twin has still not quit. The Cox proportional hazards model (Cox 1972) is a flexible and semi-parametric regression model that models the duration until quitting for the 2nd twin while simultaneously dealing with the censoring problem.

$$h_i(t) = h_0(t)\exp(\beta_1 x_{i1} + \beta_2 x_{i2} + ...\beta_k x_{ik}) \qquad (1)$$

$$\eta_i = \beta_1 x_{i1} + \beta_2 x_{i2} + ...\beta_k x_{ik}\,. \qquad (2)$$

The most basic model is presented in equation 1 which specifies the hazard for the ith pair as a function of duration. This model does not specify the form of the baseline hazard and the covariates (x1, x2, xk, etc.) influence the hazard linearly. As such, the linear prediction for the i*th* pair is given in equation 2. The ratio of the linear prediction for observation a and observation b is known as the hazard ratio (e.g, e^{η_a} / e^{η_b}) which is why this model is generally referred to has a proportional hazards model. We use the package *coxph* (Therneau and Lumley 2009) in R 2.90 to estimate all proportional hazards models.

As described above, we expect greater concordance in smoking cessation among MZ compared to DZ twins, thus we expect a positive and significant slope for the dummy variable coded MZ=1 and DZ=0. Importantly, we also expect that the magnitude of this coefficient will be higher in the later half of our study window (e.g., 1970-1980). Accordingly, we estimate three Cox proportional hazards models: a) full sample (n = 596); b) those who quit between 1960 and 1970 (n = 281); and c) those who quit between 1971 and 1980 (n = 315). We expect a negligible effect of zygosity for the first period

and a large and significant effect for the second period. These estimates are presented in Table 2.

We then estimate similar models for each year of our study between 1960 and 1980. Because of small sample sizes for year of first cessation in our study, we calculate time-specific estimates for a moving sample with a window of 2 years. For example, a sample for 1970 includes pairs in which the first to quit occurred between 1968 and 1972. These estimates are presented in Table 3.

Results

[TABLE 1 ABOUT HERE]

Table 1 presents the first evidence for greater concordance of smoking desistence among MZ compared to DZ twins. Of the 363 MZ pairs in which both reported to be regular smokers and in which one member quit during the years 1960-1980, the other member of the pair quit within two years 14.9% (n = 54) of the time. This same number is only 9.4% for DZ pairs. On average, MZ pairs quit within 10 years of one another but this number increases to 11 years among DZ pairs. Both associations are significant (p~ .05).

[TABLE 2 ABOUT HERE]

Table 2 presents the results from three Cox proportional hazards models using the full samples and then examining the association by decade of desistence. As described above, an attempt to adjust for age and cohort influences is evident in the statistical controls for year of birth, difference in years in which the members of the pair began smoking, the age at which the target person started smoking, and the age at which the

first member of the pair quit smoking. The primary parameter of interest is the coefficient for MZ ($b = .224$, $p < .05$). This positive and significant coefficient suggests that MZ pairs are a "greater risk" of quitting in a shorter period of time (after their sibling quit) compared to DZ pairs. In other words, MZ pairs exhibit a greater concordance for smoking desistence than do same-sex DZ pairs; we take this excess concordance as tentative evidence for genetic influences on this complex phenotype.

Importantly, this same model is repeated for pairs in which the first twin to quit did so between 1960 and 1970 and those in which the first twin to initiate quitting did so between 1971 and 1980. As shown here, the positive and significant coefficient in the first model is an average genetic influence across the two periods but this masks the observation that there is little evidence for genetic influences in the first period ($b = .126$, n.s.), but markedly higher influence for the second period ($b = .359$, $p <.05$). These findings provide strong support for the social push hypothesis described above.

[TABLE 3 ABOUT HERE]

[FIGURE 1 ABOUT HERE]

To further explore period influence on the genetics of smoking desistence, we then repeated this model for each year between 1960 and 1980. Using a moving window of 2 years (see Table 3 and Figure 1), these results further support the social push hypothesis for smoking desistence. As hypothesized, the first upward tick in the genetic influences on smoking desistence occur following 1973, the year in which the first formal restrictions of smoking in public places. Although the price of cigarettes increased due to increased excise taxes and evidence regarding the health risks were widespread, this was the first time at which smoking behaviors were sanctioned and limited. Therefore, while

these controls may dampen the genetic influences on smoking initiation, they may actually increase the extent to which genetic risk characterizes the composition of the at-risk population. Because of these compositional changes, our results, suggest that 1975 was one of the first years in which genetic influences were observable for smoking desistence.

Discussion

It is increasingly obvious that a complete understanding of complex behaviors such as smoking and smoking desistence requires detailed information about biological and social factors. Previous research has show that regular smoking is highly heritable but recent work has shown that heritability estimates are contingent upon social and institutional characteristics of the environment (Timberlake et al. 2006; Boardman et al. 2008, Boardman 2009). We do not find evidence for the social control model for smoking desistence. That is, legislative efforts and increased taxes on cigarettes did not reduce the heritability of smoking desistence. We did, however, present evidence supporting the social push model in which increasing social controls changed the composition of smokers such that those who remained in the smoking population were more distinguished more by genetic vulnerability than those in previous years.

We add on the existing gene-environment interplay literature in two ways. First, we build on similar work of others (Kendler et al. 2000; Boardman et al. 2010) and we demonstrate that historical time periods can be characterized as discrete social environments that moderate genetic influences on behavior. This point is made by Rutter (2006:60) who argues that "there is not, and cannot be, any absolute value for the strength of genetic influences on a trait" and "heritability figures are necessarily specific to populations and

to time periods. Despite the support for this perspective among leading genetic epidemiologists, little work has been done to specify the mechanisms responsible for periodic highs and lows in social vs. genetic causes for health behaviors in the population. In this paper, temporal changes in the genetic epidemiology of smoking are carefully linked to smoking norms, the costs of smoking, and legal limits placed upon smokers. This context provides a useful background to evaluate existing gene-environment interaction theory. Importantly, these findings suggest that current efforts to characterize genetic influences on behaviors like smoking should be careful to consider that the samples are drawn from populations at a particular moment in a smoking trend. That is, suppose a sample of 1000 regular smokers was taken in 2009 and then followed to monitor their smoking duration, quit attempts, and successful desistence. If researchers, used family based association methods across the human genome to predict successful quitting, it is possible that very few or even a different set of SNPs would be identified if this same study had been done in 1960. That is, not only does it appear that the heritability for smoking desistence was smaller in the 1960s compared to the 1970s thus comprising the likelihood of identifying causal loci, but the composition of smokers changed and SNPs linked to smoking desistence in the 1960s may be quite different from those in later decades.

Second, we extend this literature by considering smoking desistence as the primary smoking phenotype. Although the heritability of successful quitting is shown to be roughly .40 (Xian et al. 2003), there remains very little behavioral genetic research on smoking desistence and almost no work has examined gene-environment interactions with respect to the likelihood that a current smoker will quit. We argue that this phenotype is more closely linked to physiological processes associated with nicotine addiction and that zygosity differences in the concordance of quitting, as opposed to

concordance in smoking onset, sheds new light on this complex issue. This is important because entry in to smoking draws from the general population but exit from smoking draws from the regular smoking population. This is a continuously changing population thus the most reticent to exit from smoking status may also be those for whom symptoms of nicotine withdrawal are felt most acutely. This has important implications for case-control studies, because over time, cases may be an increasingly select group of people compared to controls who are drawn from a much larger pool of people. In other words, even under the most strict association models, identifying causal genetic factors may be somewhat problematic for behaviors like smoking with clear social trends.

This perspective helps to account for the differences observed in the Boardman et al. (2010) paper in which the authors show that the heritability of the *onset* of regular smoking decreases in the mid 1970s. Not only are these different phenotypes, but the social mechanisms for entry and exit are very different. Similarly, genes implicated in smoking onset are quite different from smoking desistence (Broms et al. 2006). As such, it is not surprising that the period effects on the genetics of smoking desistence are different as well. It is well known that genes linked to novelty seeking and risk taking are associated with smoking onset, whereas smoking desistence and successful quitting are strongly associated with loci that regulate nicotine metabolism (Lerman et al. 1999; Erhniger et al. 2007). Therefore, social policies designed to address the social and genetic epidemiology of smoking need to be clear about the etiology of these different smoking phenotypes. That is, effective smoking policy needs to consider the current location within a particular trend when developing effective policies. Social policy affects the prevalence but it also differentially affects the trade off between social and genetic

causes of the behavioral phenotype; the causes of entry, exit, and continuation into the smoking population are likely to be very different over time so the policies should adjust accordingly. Exit from the smoking population in the 1960s was more likely dealt with by policies targeting social norms of smoking, perceived health risks, and increased costs of smoking. However, if genetic factors are increasingly important then current policies designed to assist people in quitting should be aimed more specifically at the physiological and social-psyschological mechanisms of addiction.

Conclusion

Clinical and psychological scholarship has progressed over the years to the point where it is now well understood that genetic diversity is one of the components that contributes to differences between humans and to risk for substance use disorders, including, smoking onset, amount of smoking, and smoking desistance (Li et al. 2003). But genetic factors are clearly not the entire story. The social and the physical environment, the interaction between parent and child, peers, role models, and the macro environment, such as public policy, are clearly and demonstratively important in human variability. This paper improves our ability to integrate the effects of social policy and genetic risk for complex behavior such as smoking. Initiation of smoking, age of onset, addiction, reward and penalty all differentially influence whether one is a smoker or not. In the analyses presented here, we have demonstrated a new approach in the investigation of genetic contributions to smoking desistence by showing that the macro environment, measured by policy change, changes how we can identify those at most risk for continued tobacco smoking. Because this approach treats the biometric analyses of smoking desistance as an interaction between person and macro environment as well as individual

environment, it provides more information on how to better identify the influence of genes in determining variation in smoking desistance.

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Table 1. Pairwise concordance in the timing of smoking desistence by zygosity.

	MZ	DZ
Quit (1960-1980)		
Total N	363	233
Quit within 2 years	54	22
Proportion	0.149	0.094
Chi-square	3.77, df=1, p<.051	
Mean years difference	10.08	11.02
	(6.79)	(6.57)
Ttest	1.65, df=594, p<.049	

Note: Data on twin pairs come from a large population-based birth registry for the Commonwealth of Virginia and the American Association of Retired Persons. See Truett et al. (1994) and Eaves et al. (1999) for additional information about this study. This study only uses data in which both members of the twin pair report regular smoking at some point during the study.

Table 2. Zygosity differences in the duration to smoking desistence following co-twin desistence by period.

	Full		1960-1970	1971-1980	
Year of birth	0.021	*	0.012	0.032	
	(.010)		(.024)	(.031)	
Gender [Male]					
Female	-0.065		-0.057	-0.094	
	(.108)		(.146)	(.161)	
Zygosity [DZ]					
MZ	0.224	*	0.126	0.359	*
	(.110)		(.150)	(.166)	
Difference in start	-0.029	*	-0.019	-0.052	+
	(.014)		(.017)	(.027)	
Age started (2nd quit)	0.005		-0.004	0.027	
	(.013)		(.016)	(.022)	
Age first quit	0.027	*	0.022	0.036	
	(.011)		(.024)	(.031)	

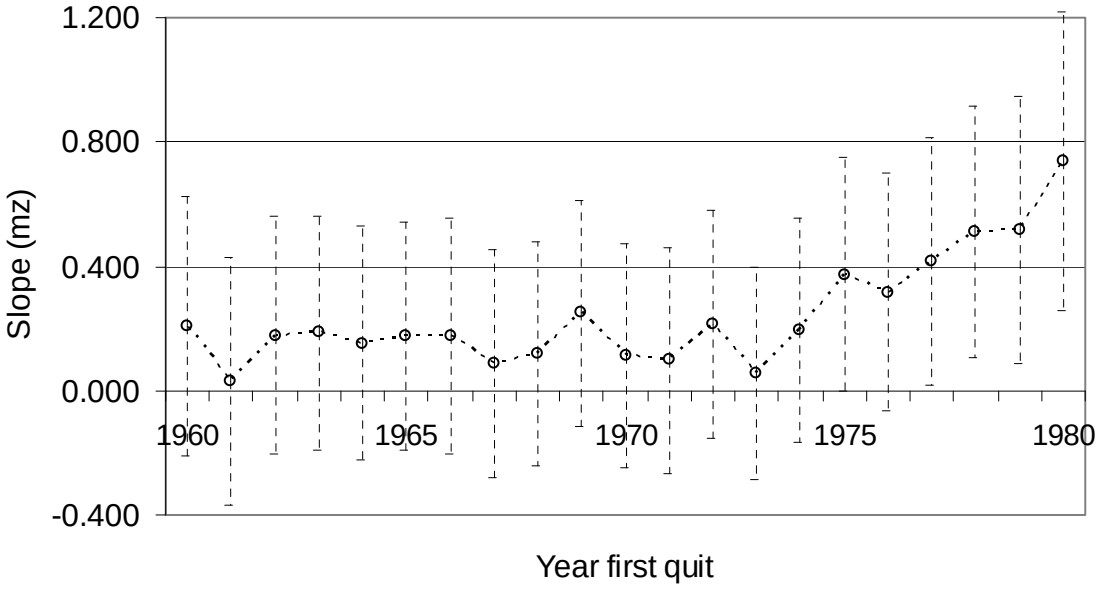
Note: Data on twin pairs come from a large population-based birth registry for the Commonwealth of Virginia and the American Association of Retired Persons. See Truett et al. (1994) and Eaves et al. (1999) for additional information about this study. This study only uses data in which both members of the twin pair report regular smoking at some point during the study and in which one member of the pair reports quitting. Cell entries are Cox proportional hazards estimates which describe similarity in the timing of smoking desistence.

Table 3. Yearly Cox PH model estimates for the duration of smoking discordance.

Year	b	se	z	pr	LR	pr
1960	0.208	0.214	0.971	0.332	0.962	0.327
1961	0.033	0.203	0.161	0.872	0.026	0.871
1962	0.177	0.194	0.913	0.361	0.845	0.358
1963	0.187	0.192	0.973	0.331	0.961	0.327
1964	0.152	0.191	0.794	0.427	0.638	0.424
1965	0.175	0.188	0.929	0.353	0.875	0.350
1966	0.178	0.194	0.917	0.359	0.855	0.355
1967	0.088	0.187	0.470	0.638	0.223	0.637
1968	0.117	0.185	0.635	0.525	0.407	0.523
1969	0.248	0.186	1.334	0.182	1.821	0.177
1970	0.110	0.184	0.600	0.548	0.363	0.547
1971	0.097	0.185	0.526	0.599	0.279	0.597
1972	0.214	0.188	1.135	0.256	1.315	0.251
1973	0.055	0.175	0.316	0.752	0.100	0.752
1974	0.194	0.183	1.060	0.289	1.139	0.286
1975	0.374	0.191	1.953	0.051	3.944	0.047
1976	0.318	0.194	1.636	0.102	2.753	0.097
1977	0.416	0.202	2.059	0.040	4.413	0.036
1978	0.513	0.207	2.481	0.013	6.463	0.011
1979	0.517	0.220	2.347	0.019	5.826	0.016
1980	0.738	0.246	2.995	0.003	9.860	0.002

Note: Data on twin pairs come from a large population-based birth registry for the Commonwealth of Virginia and the American Association of Retired Persons. See Truett et al. (1994) and Eaves et al. (1999) for additional information about this study. This study only uses data in which both members of the twin pair report regular smoking at some point during the study and in which one member of the pair reports quitting. Cell entries are Cox proportional hazards estimates which describe similarity in the timing of smoking desistence by the year in which the first member of the pair initiated quitting. See text for a full description of the methods used to calculate the parameter estimates.

Figure 1. Yearly changes in the genetic influences on smoking desistence.



Note: Estimates derived from Table 3. See text for a full description of the methods used to calculate the parameter estimates.