

Figure SF1: Flow Chart of Available Sample, Measures Utilized, Missing Data at Each Wave, and Years During Which Each Cohort Was Assessed

^aBecause ADHD was not re-assessed in Cohort 1 at either follow-up, only childhood ADHD data at baseline was utilized for this report.

^bData for 96.5% of the full baseline sample of 3762 twins (N = 3629) was available for survival analyses of age of initiation because some participants missing a follow-up reported initiation had occurred by either the age 11 or 14 visit.

**Hazard Functions for Tobacco Initiation in
Discordant MZ Twin Pairs with a 4 – 6 or 7+ Symptom
Within-Pair Difference in ADHD**

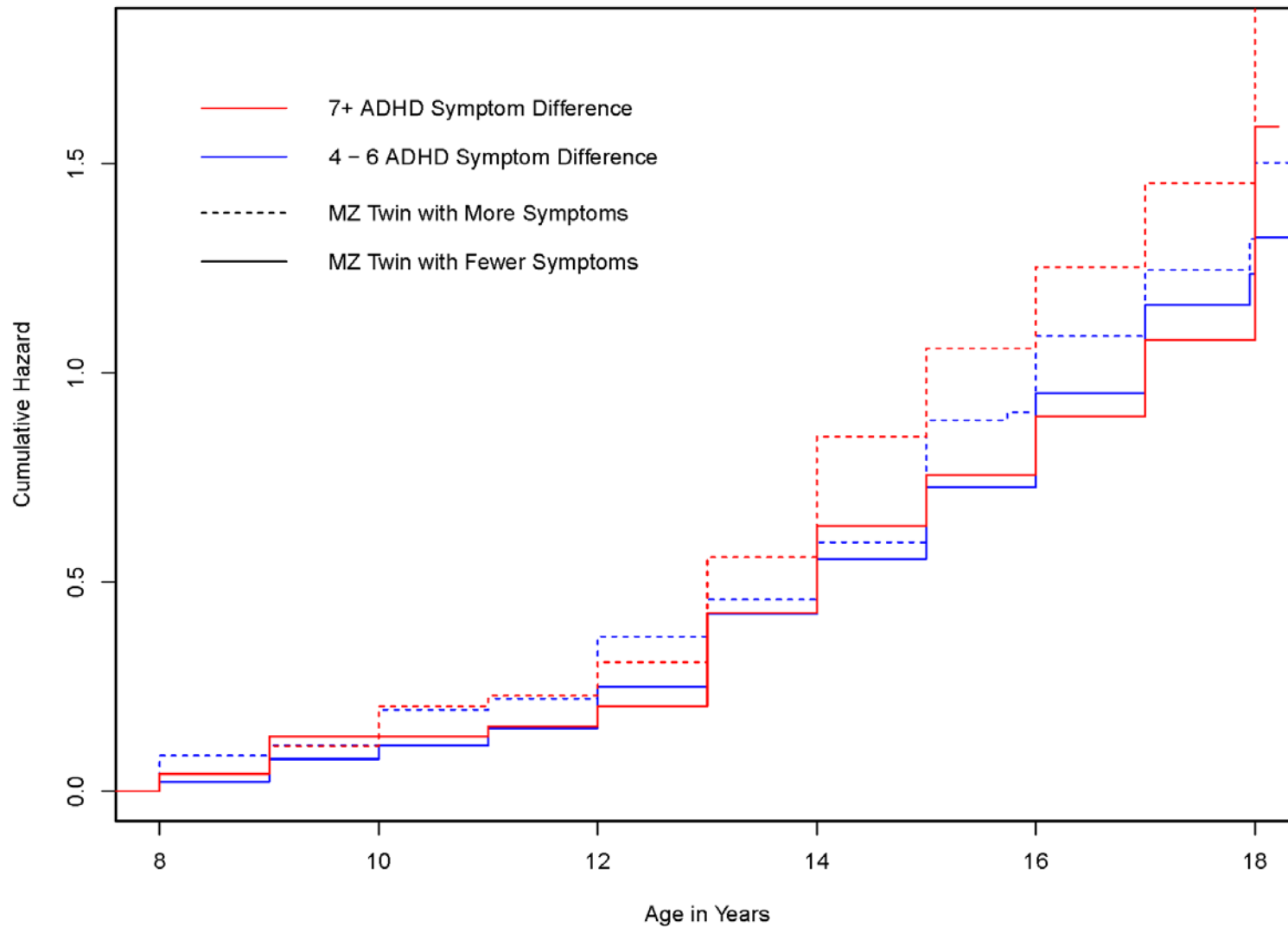


Figure SF2: Cumulative Hazard for Smoking Initiation in 185 Male and Female MZ Twin Pairs Discordant for ADHD

Note: Blue lines represent the 136 MZ pairs who differed by 4-6 symptoms (a within-pair difference of approximately 1-2 SDs); red lines represent the 49 MZ pairs who differed by 7 or more symptoms (2+ SDs). Dotted lines represent the twin in each pair with more ADHD symptoms; solid lines represent the less affected twin. With increased age, differences in rate of initiation between co-twins more (dotted lines) and less affected (solid lines) by ADHD increased in magnitude and were especially apparent among the most discordant pairs.

Table ST1: Within-Pair Difference Effects of Baseline ADHD Symptoms on Smoking Initiation, Progression to Daily Smoking, Cigarettes Per Day, and DSM-IV Nicotine Dependence by Age 17 - For Combined Sample of All MZ and DZ Twin Pairs

	Inattentive Symptoms (raw- or z-score)			Hyperactive-Impulsive Symptoms (raw- or z-score)		
Smoking Involvement by Age 17	All Complete Pairs N=1806 pairs					
<i>Initiation of Use - age in years^a</i>	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
	1.07	1.03, 1.11	<0.0001	1.07	1.02, 1.12	<0.001
<i>Progression to Daily Smoking^a</i>	All Pairs N=1709 (891 female; 818 male)					
	Odds Ratio	95% CI	p	Odds Ratio	95% CI	p
	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>
	1.15	1.05, 1.26	<0.001	1.29	1.16, 1.45	<0.0001
	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>
	1.04	0.96, 1.13	NS	0.98	0.88, 1.08	NS
<i>Maximum Cigarettes Per Day(z)^b</i>	All Pairs N=1694 (886 female; 808 male)					
	β	95% CI	p	β	95% CI	p
	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>
	.13	.08, .18	<0.0001	.17	.11, .23	<0.0001
	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>
	-.01	-.06, .04	NS	-.03	-.09, .03	NS
<i>Symptoms of Nicotine Dependence(z)^b</i>	All Pairs N=1709 (891 female; 818 male)					
	β	95% CI	p	β	95% CI	p
	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>	<u>Female</u>
	.13	.08, .19	<0.0001	.16	.09, .22	<0.0001 DZ>MZ^c
	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>	<u>Male</u>
	.01	-.04, .07	NS	-.03	-.09, .03	NS

^aEffects for initiation are given as hazard ratios; effects for progression to daily smoking are given as odds ratios. Those significantly greater than 1.0 correspond to the increased likelihood of initiating at each age (ages 8-18) or progressing a level toward daily smoking associated with a 1 symptom increase in ADHD. Within-pair estimates reflect differential likelihood of initiating or progressing in frequency associated with a twin having 1 more ADHD symptom than his or her co-twin.

^bEffects for CPD and nicotine dependence are given as standardized beta coefficients (β), because ADHD symptoms, CPD, and log-transformed nicotine dependence symptoms were all converted to standardized (z) scores. Individual-level estimates reflect the increase in CPD or symptoms (in SD units) associated with a 1 SD increase in ADHD; within-pair estimates reflect the difference (in SD units) associated with a twin being 1 SD higher in ADHD than his or her cotwin.

^cDZ>MZ indicates that the within-pair effect was significantly greater for DZs than MZs ($p < .05$).

Appendix SA1: Information Regarding the Statistical Analysis and Treatment with Stimulants

Power estimates in the Method were based on calculations assuming an average MZ twin correlation in smoking outcomes of .60, a comparable correlation for ADHD, and approximately 1100 MZ pairs with outcome data. Twin difference analyses decomposed each individual's ADHD symptoms (either inattentive or hyperactive-impulsive, depending on the model) into shared, between-pair (i.e., pair average) and non-shared, within-pair effects on smoking (Begg and Parides; 2003). Correlation within pairs was accounted for by a random intercept at the cluster (pair) level, except for survival models, which used a shared frailty term (Sjolander et al., 2013). Our approach was consistent with that described by Carlin as "Multiple Regression: Including the Co-twin X Value in the Model" (Carlin et al., p. 1092). There are different ways this regression model can be expressed that lead to different interpretations of the between-pair effect, while the within-pair effect remains essentially the same (cf. Begg and Parides; 2003).

For analyses determining whether twin differences in conduct/oppositional defiant disorders (or stimulants) mediated potentially causal effects of inattention on smoking for females, we consulted the multilevel models of mediation profiled by Zhang et al. (2009). Determining whether the non-shared exposure effect (i.e., inattention) is mediated requires assessing whether the deviation term for inattention remains significant after the deviation term for the potential mediator is added. Omitting covariates and the between-pair term included in the twin difference analyses described above, this may be represented by the equation below, where Y_{ij} is the expected smoking outcome for a given individual twin i in twin pair j . X_{ij} represents inattention symptoms for twin i , from which the mean number of inattention symptoms for the pair was subtracted, creating the within-pair deviation term for inattention for twin i . The additional within-pair deviation term (b_2) is based on twin i 's score on the potential mediator (M_{ij}), from which the mean score on the mediator for the pair was subtracted: $\hat{Y}_{ij} = b_0 + b_1(X_{ij} - \bar{X}_{.j}) + b_2(M_{ij} - \bar{M}_{.j})$

Treatment with Stimulant Medications: Stimulant medication use included both methylphenidate- and amphetamine-based formulations. Use of these medications was reported for 225 twins at baseline or follow-up. For the clinically-relevant ADHD cases described in the Method, those treated with stimulant medications (N=155) had more ADHD symptoms (M = 11.6; SD = 3.0) than those never medicated [M = 9.1; SD = 2.6; $t(536) = 9.65, p < .0001$], highlighting the importance of controlling for baseline ADHD symptoms in analyses regarding the effects of stimulants on substance use, as suggested by Looby (2008).

References

Begg, M.D. and M.K. Parides, *Separation of individual-level and cluster-level covariate effects in regression analysis of correlated data*. *Statistics in Medicine*, 2003. **22**(16): p. 2591-2602.

Carlin, J.B., et al., *Regression models for twin studies: a critical review*. *Int J Epidemiol*, 2005. **34**(5): p. 1089-99.

Looby, A., *Childhood attention deficit hyperactivity disorder and the development of substance use disorders: valid concern or exaggeration?* *Addict Behav*, 2008. **33**(3): p. 451-63.

Zhang, Z., M.J. Zyphur, and K.J. Preacher, *Testing Multilevel Mediation Using Hierarchical Linear Models Problems and Solutions*. *Organizational Research Methods*, 2009. **12**(4): p. 695-719.