



Correlates of nicotine dependence in men with childhood attention-deficit/hyperactivity disorder: a 33-year follow-up

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Abstract

Identify correlates of nicotine dependence [lifetime (l) and ongoing (o)] in adults with attention-deficit/hyperactivity disorder (ADHD) in childhood. We conducted a 33-year prospective follow-up of boys (mean age 8) with combined type ADHD ($n = 135/207$, 65% original sample). Correlates of nicotine dependence in adulthood were selected from characteristics obtained in childhood and adolescence. Among selected childhood features, only immature behavior was significantly related to nicotine dependence ($OR_{(o)} = 0.29$, $p = 0.02$), indexing decreased risk. In contrast, several adolescent variables significantly correlated ($p < 0.01$) with nicotine dependence at mean age 41, including alcohol substance use disorder (SUD, $OR_{(l)} = 4.97$), non-alcohol SUD ($OR_{(o)} = 4.33/OR_{(l)} = 10.93$), parental antisocial personality disorder ($OR_{(l)} = 4.42$), parental SUD ($OR_{(l)} = 3.58$), dropped out of school ($OR_{(l)} = 2.29$), impulsivity ($OR_{(o)} = 1.53/OR_{(l)} = 1.59$), hyperactivity ($OR_{(o)} = 1.38$), and number of antisocial behaviors ($OR_{(o)} = 1.10/OR_{(l)} = 1.14$). Results highlight the role of adolescent psychopathology in the development of nicotine dependence, motivating prospective longitudinal efforts to better define the developmental trajectories of risk and protection.

Keywords ADHD · Prediction · Nicotine dependence · Longitudinal method

Introduction

Tobacco remains the leading cause of preventable disease and death worldwide, causing approximately six million deaths and economic damage exceeding a half trillion dollars per year (World Health Organization 2013). Although

rates of smoking have declined, the prevalence of daily smoking in the USA remains about 18% in the general adult population (42 million) (Centers for Disease Control and Prevention 2014). Nearly all (90%) adult smokers began smoking before 18 years of age, and 99% before 26 (U.S. Department of Health and Human Services 2014). Accordingly, childhood and adolescence represent optimal periods for preventive efforts.

Longitudinal studies have demonstrated an association between childhood ADHD and nicotine substance use disorder (Charach et al. 2011; Klein et al. 2012; Lee et al. 2011). Despite this well-established relationship, the childhood correlates of adult nicotine dependence among individuals with ADHD remain unclear. In a population sample of children, ratings of inattention, but not of hyperactivity, predicted nicotine dependence in late adolescence (Pingault et al. 2013), whereas among children diagnosed with ADHD, symptoms of hyperactivity/impulsivity, and to a lesser extent inattention, were significant predictors (Elkins et al. 2007). However, some studies (Burke et al. 2001; Fergusson et al. 2007), but not all (Elkins et al. 2007), have noted that the relationship between childhood ADHD symptoms and

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later nicotine dependence is due to the primary effect of co-existing conduct problems and that ADHD symptoms per se do not confer additional risk. Finally, one study reported a linear positive relationship between self-ratings of inattention and hyperactivity/impulsivity in adolescence and the number of nicotine dependence symptoms in young adulthood (Rodríguez et al. 2008).

In the longest prospective longitudinal follow-up of children with combined type ADHD, followed over a 33-year span from mean ages 8–41, ongoing nicotine dependence was significantly more prevalent in probands with childhood ADHD than in comparisons (30% vs. 9%, $p < 0.001$) (Klein et al. 2012). Our aim in the present analysis was to focus on the probands with childhood ADHD to identify early predictors of nicotine dependence in middle adulthood. We hypothesized that selected measures obtained in childhood and adolescence would predict significantly elevated rates of nicotine dependence. We also hypothesized that participants with an ongoing diagnosis of ADHD at mean age 41 (i.e., those with persistent ADHD) would have significantly elevated rates of ongoing nicotine dependence, relative to those who no longer met criteria for ADHD.

Methods

Participants were 207 Caucasian boys, initially recruited at ages 6–12 years (mean 8.3 ± 1.6 years), from middle and lower-middle class, who had been referred to a psychiatric research clinic by schools between 1970 and 1978 because of behavior problems. Inclusions were: a current and previous history of behavior problems at home and school, verbal $IQ \geq 85$, elevated teacher and parent ratings of hyperactivity, and English-speaking parents. Children with neurological or significant medical disorders, or psychosis were excluded. To minimize confounding effects of conduct disorder, children with a pattern of aggressive, or other antisocial, behaviors were also excluded. Based on a clinical examination of the child and parent, child psychiatrists completed currently accepted assessments of the child's clinical history and behavior from direct examination. Children were administered cognitive tests that included the Wechsler Intelligence Scale for Children (WISC) (Wechsler 1974). Original sample characteristics have been presented elsewhere in detail (Gittelman et al. 1980; Gittelman-Klein and Klein 1975; Gittelman-Klein et al. 1976a, b).

In late adolescence, when children were on average 18, they were reassessed [(Follow-Up 18, FU18) (mean age, 18.1 ± 1.3 ; $n = 195/207$, 94% retention)] (Gittelman et al. 1985). Adolescents and parents were interviewed by doctoral-level psychologists, blind to all antecedent data. Participants were evaluated using the Teenager or Young Adult Schedule (TOYS), a modified clinical version of the

NIMH Diagnostic Interview Schedule (DIS) (Mannuzza et al. 1991; Robins et al. 1981). Information about the adolescents was obtained by interviewing parents using reworded TOYS items (Parent interview, or PARI). The interviews inquired about multiple functions between 16 and 18 years of age, and beyond 18. In this study, adolescent predictors reflect functioning between ages 16 and 18 years. Parental psychopathology was assessed using the DIS and/or the spouse interview schedule. A subsequent follow-up, at mean age 25, has been reported (Mannuzza et al. 1993, 1998). Nicotine dependence was not assessed at FU25, so the data from this wave are not considered in this report.

The last follow-up occurred, on average, 33 years after initial referral when participants' mean age was 41.4 ± 2.9 years [(range 35–47) (Follow-Up 41, FU41)]. We obtained information on 135 of the original 207 participants (65.2%). Characteristics of assessed and lost probands did not differ significantly in childhood, nor at FU18 (Klein et al. 2012). Trained clinicians, blind to all previous data, conducted semi-structured clinical interviews, inquiring about functioning since the person's last assessment, using the non-patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (First 2002). Detailed information about the sample and instruments at FU41 is reported elsewhere (Klein et al. 2012). Nicotine dependence was assessed at FU41 recollecting DSM-IV criteria (American Psychiatric Association 1994) and with inquiry about multiple aspects of tobacco use. To maintain consistency with prior reports (Klein et al. 2012; Mannuzza et al. 2011; Ramos Olazagasti et al. 2013), we continue to use DSM-IV criteria when applicable. These criteria were applied for the diagnoses of lifetime and ongoing nicotine dependence (ongoing defined as during the last 6 months).

Two authors (RGK, FXC), expert in ADHD, identified possible correlates based on the literature and their clinical relevance. The final roster of childhood factors consisted of: parents' socioeconomic status; children's full scale IQ, reading level; ratings of social functioning, ADHD severity, conduct problems, oppositional defiant behaviors, eruptive aggression, and immature behavior (see Table 1). Age of first cigarette use was also included as a correlate.

Correlates from adolescent assessments (present between ages 16 and 18, see Table 2) included: clinician ratings of impairment due to inattention, hyperactivity, and impulsivity; ratings of global job functioning and global social functioning, as well as a diagnosis of non-alcohol substance use disorder (SUD), having dropped out of school prior to high school graduation, number of antisocial behaviors, work goals, educational goals, parental SUD, and parental antisocial personality disorder (APD).

Table 1 Childhood predictors: description, scoring, and number rated

Childhood predictors	Description	Scoring (min–max)	<i>N</i>
Parental SES	Socioeconomic status (Hollingshead and Redlich)	1 = lower class to 5 = upper class	135
WISC	Wechsler Intelligence Scale for Children (Full scale IQ)	Standard score	135
WRAT-reading	Wide range achievement test	Standard score	135
ADHD severity	Mean of nine Conners Teacher Rating Scale (CTRS) items	0 = not at all 3 = very much	135
Conduct problems	Mean of four CTRS items and 12 Conners Parent Rating Scale (CPRS) items	0 = not at all 3 = very much	135
Oppositional behavior	Mean of eight CTRS items and eight CPRS items	0 = not at all 3 = very much	135
Eruptive aggression	Psychiatrist rated: “unable to control response toward peers/adults. Physically aggressive, impulsive, often reacts to others before understanding the meaning or motives of their words or actions. Gets into numerous fights. Physically disruptive particularly in classroom where he may hit out at others with little or no provocation”	0 = absent 1 = present	113
Immature behavior	Psychiatrist rated: “immature/inadequate behavior with poorly organized personality characteristics and coping techniques”	0 = absent 1 = present	115
Social factor score	Mean of four CTRS items	0 = not at all 3 = very much	135

min minimum, *max* maximum, *N* number of participants rated

Table 2 Adolescent predictors: description, scoring, and number rated

Adolescent predictors	Description	Scoring (min–max)	<i>N</i>
Dropped out of school	Dropped out of junior high or high school, even if graduated later	0 = absent; 1 = present	131
Severity of inattention	Clinician rating, ages 16–18	1 = none/mild–5 = extreme	131
Severity of hyperactivity	Clinician rating, ages 16–18	1 = none/mild–5 = extreme	131
Severity of impulsivity	Clinician rating, ages 16–18	1 = none/mild–5 = extreme	131
Number of antisocial behaviors	25 discrete antisocial behaviors at school, home and other settings from self and parent reports	0 = absent–25 = all present	131
Non-alcohol substance use disorder	Ongoing DSM–III diagnosis	0 = absent; 1 = present	131
Educational goals	Clinician rating based on self-report by participant	1 = has little or no idea 4 = specific goals in mind	119
Work goals	Clinician rating based on self-report by participant	1 = has little or no idea 4 = specific goals in mind	121
Global job functioning	Clinician rating based on self-report by participant	1 = poor–6 = superior	123
Global social functioning	Clinician rating based on self-report by participant	1 = poor–6 = superior	131
Parental alcohol/non-alcohol substance use	Lifetime diagnosis based on DIS or SIS	0 = absent–1 = present	114
Parental antisocial personality disorder	Lifetime diagnosis based on DIS or SIS	0 = absent–1 = present	114

min minimum, *max* maximum, *DIS* Diagnostic Interview Schedule, *SIS* spouse interview schedule

Data analysis

Logistic regressions were used to model the odds of having an ongoing or lifetime diagnosis of nicotine dependence at mean age 41 from childhood and adolescent correlates. Due to the heuristic nature of the study and to maximize interpretability, each predictor was examined in a separate model. Chi-square tests contrasted rates of

nicotine dependence in groups with and without lifetime ADHD. Alpha was set at .05, two tailed.

Results

At mean age 41 years, 41 (30%) of the 135 probands with childhood ADHD had ongoing nicotine dependence (Klein et al. 2012). Of those 135 probands, 69 (51%) had a lifetime

history of nicotine dependence, with mean age of first cigarette use at 15.2 ± 4.6 (range 5–25 years), and mean age of first regular cigarette use at 17.2 ± 3.9 (range 9–30 years). At some time, 117 (87%) had used nicotine (108 smoked cigarettes, others smoked cigars, etc.) and 28 probands with a previous history of nicotine dependence had stopped smoking on average at age 33.9 ± 7.4 (range 16–47).

Thirty of the 135 participants (22%) received an ongoing DSM-IV diagnosis of ADHD at FU41. An additional 36 (27%) had symptoms of ADHD that impaired function significantly, but the number of ADHD symptoms fell below DSM-IV threshold for the diagnosis (i.e., less than 6 symptoms of either inattention, or hyperactivity/impulsivity); 69 (51%) participants were free of any impairing symptoms of ADHD at FU41. Prevalence of ongoing nicotine dependence did not differ significantly across these three groups ($\chi^2(2) = 3.46, p = 0.18$).

Tables 3 and 4 present risks for ongoing and lifetime nicotine dependence in middle adulthood as a function of child and adolescent correlates. As shown in Table 3, the only childhood characteristic that predicted nicotine dependence significantly was the psychiatrist's rating that behavior was immature and only for ongoing nicotine dependence.

Contrary to expectation, a rating of immaturity protected against ongoing nicotine dependence in adulthood, as reflected by an odds ratio well below 1.00 ($OR = 0.29$).

Among the adolescent predictors, severity of impulsivity and number of antisocial behaviors were significantly associated with ongoing (o) and lifetime (l) nicotine dependence in adulthood ($OR_{(o)} = 1.53/OR_{(l)} = 1.59, OR_{(o)} = 1.10/OR_{(l)} = 1.14$, detailed in Table 4). The presence of non-alcohol substance use disorder in adolescence was the strongest predictor of nicotine dependence in adulthood ($OR_{(o)} = 4.33/OR_{(l)} = 10.93$). Having dropped out of school, alcohol SUD, parental SUD and parental antisocial personality disorder were also correlates for lifetime nicotine dependence (OR 's 2.29, 4.97, 3.58 and 4.42, respectively). In the case of ongoing nicotine dependence, hyperactivity was also a statistically significant correlate ($OR_{(o)} = 1.38$).

Discussion

This is the first prospective follow-up of hyperactive children with combined type ADHD that examines predictors of nicotine dependence, extending into the fourth and fifth decades

Table 3 Univariate relationships between childhood variables and ongoing/lifetime nicotine dependence at follow-up 41

Predictor (score range)	Ongoing			Lifetime		
	Non-ND ($n = 94$)	ND ($n = 41$)	Ongoing	Non-ND ($n = 66$)	ND ($n = 69$)	Lifetime
Childhood	Mean \pm SD or n (%)	Mean \pm SD or n (%)	OR (95% CI)	Mean \pm SD or n (%)	Mean \pm SD or n (%)	OR (95% CI)
Parental SES (1–5)	2.9 \pm 1.1	2.6 \pm 1.0	0.74 (0.50–1.07)	2.9 \pm 1.1	2.7 \pm 1.0	0.76 (0.55–1.06)
WISC IQ (standard score)	104.43 \pm 12.34	103.59 \pm 12.35	0.99 (0.96–1.02)	104.92 \pm 13.46	103.45 \pm 11.14	0.99 (0.96–1.02)
WRAT-reading (standard score)	101.17 \pm 17.42	100.95 \pm 17.14	1.00 (0.98–1.02)	101.61 \pm 18.99	100.62 \pm 15.57	1.00 (0.98–1.02)
ADHD severity (0–3)	2.31 \pm 0.44	2.21 \pm 0.45	0.62 (0.27–1.4)	2.26 \pm 0.46	2.29 \pm 0.43	1.78 (0.55–2.53)
Conduct problems (0–3)	0.70 \pm 0.44	0.64 \pm 0.35	0.81 (0.32–2.10)	0.66 \pm 0.39	0.69 \pm 0.43	1.56 (0.65–3.73)
Oppositional behavior (0–3)	1.66 \pm 0.57	1.49 \pm 0.61	0.59 (0.31–1.12)	1.62 \pm 0.60	1.59 \pm 0.58	0.92 (0.52–1.64)
Eruptive aggression (yes/no)	40 (50)	15 (45)	0.83 (0.37–1.88)	26 (47)	29 (50)	1.11 (0.53–2.33)
Immature behavior (yes/no)	31 (38)	5 (15)	0.29 (0.10–0.84)**	20 (35)	16 (27)	0.70 (0.32–1.56)
Social factor score (0–3)	1.96 \pm 0.77	2.05 \pm 0.63	1.20 (0.72–2.01)	1.95 \pm 0.75	2.02 \pm 0.70	1.15 (0.72–1.84)
Age first used cigarettes	14.46 \pm 4.06	15.24 \pm 4.61	1.04 (0.95–1.14)	14.97 \pm 4.29	14.64 \pm 4.29	0.98 (0.89–1.08)
Age first used cigarettes regularly	15.48 \pm 3.48	17.23 \pm 3.86	1.14 (1.01–1.30)	15.88 \pm 3.40	16.41 \pm 3.84	1.04 (0.89–1.21)

Non-ND no ongoing nicotine dependence, ND ongoing nicotine dependence (past 6 months), SD standard deviation, OR odds ratio, SUD substance use disorder. (Varying n 's are provided in Table 1). Statistically significant values in bold. ** $p \leq 0.01$

Table 4 Univariate relationships between adolescent variables and ongoing/lifetime nicotine dependence at follow-up 41

Predictor (score range)	Ongoing			Lifetime		
	Non-ND (<i>n</i> = 94)	ND (<i>n</i> = 41)	Ongoing	Non-ND (<i>n</i> = 65)	ND (<i>n</i> = 66)	Lifetime
Adolescence	Mean ± SD/ <i>n</i> (%)	Mean ± SD/ <i>n</i> (%)	OR (95% CI)	Mean ± SD/ <i>n</i> (%)	Mean ± SD/ <i>n</i> (%)	OR (95% CI)
Dropped out of school (yes/no)	22 (24)	15 (39)	2.10 (0.94–4.7)	13 (20)	24 (36)	2.29 (1.04–5.03)
Clinical rating of inattention (1–5)	2.39 ± 1.39	2.92	1.29 (0.99–1.67)	2.34 ± 1.33	2.74 ± 1.57	1.21 (0.95–1.54)
Clinical rating of hyperactivity (1–5)	2.03 ± 1.31	2.71 ± 1.64	1.38 (1.06–1.78)**	2.03 ± 1.26	2.42 ± 1.58	1.21 (0.95–1.55)
Clinical rating of impulsivity (1–5)	2.32 ± 1.41	3.26 ± 1.59	1.53 (1.17–1.98)**	2.09 ± 1.33	3.09 ± 1.54	1.59 (1.24–2.04)**
Number of antisocial behaviors (0–25)	9.39 ± 6.50	13.26 ± 5.37	1.10 (1.04–1.18)**	8.11 ± 6.24	12.88 ± 5.72	1.14 (1.07–1.21)**
Alcohol SUD (yes/no)	6 (6)	5 (13)	2.20 (0.63–7.69)	2 (3)	9 (14)	4.97 (1.03–23.99)**
Non-alcohol SUD (yes/no)	8 (9)	11 (29)	4.33 (1.58–11.87)**	2 (3)	17 (26)	10.93 (2.41–49.57)**
Educational goals (1–4)	2.62 ± 1.08	2.58 ± 1.00	0.96 (0.65–1.42)	2.69 ± 1.10	2.52 ± 0.99	0.86 (0.60–1.21)
Work goals (1–4)	2.83 ± 1.01	2.86 ± 0.97	1.03 (0.69–1.54)	2.83 ± 1.01	2.84 ± 0.99	1.01 (0.71–1.45)
Global job functioning (1–6)	3.77 ± 1.29	3.92 ± 1.42	1.09 (0.81–1.46)	3.62 ± 1.28	4.00 ± 1.34	1.25 (0.95–1.65)
Global social functioning (1–6)	3.41 ± 1.19	3.32 ± 1.28	0.94 (0.69–1.28)	3.48 ± 1.16	3.29 ± 1.26	0.88 (0.66–1.17)
Parental SUD (yes/no)	13 (17)*	11 (31)*	2.20 (0.87–5.55)	6 (11)*	18 (30)*	3.58 (1.30–9.87)
Parental APD (yes/no)	8 (10)*	7 (19)*	2.11 (0.70–6.36)	3 (5)*	12 (20)*	4.42 (1.18–16.65)

Non-ND no ongoing nicotine dependence, *ND* ongoing nicotine dependence, *SD* standard deviation, *OR* odds ratio, *SUD* substance use disorder, *APD* antisocial personality disorder. *Percent of parents interviewed within the ND and non-ND participants. (Varying *n*'s are provided in Table 2). Statistically significant values in bold. ** $p \leq 0.01$

of life. As previously reported (Klein et al. 2012), the 30% prevalence of ongoing nicotine dependence at age 41 was substantially higher than the 18% rate of daily smoking in the general US population (Centers for Disease Control and Prevention 2014; World Health Organization 2015).

Contrary to our hypotheses, we did not detect any childhood predictors of increased risk for nicotine dependence. Instead, immature behavior as detected by a psychiatrist was significantly related to decreased risk of adult ongoing nicotine dependence. It may be that “immature” children are more dependent on adult influence and, therefore, more rule abiding than their more mature peers. If so, “immature” children in our sample may have been reluctant to violate external expectations and, therefore, may have eschewed behaviors that are sanctioned (e.g., smoking). This interpretation is consistent with findings that experiencing romantic or sexual relationships at younger ages is associated with binge drinking, which was also associated with smoking (Whelan et al. 2014).

Not surprisingly, the strongest predictor of nicotine dependence at age 41 was the development of non-alcohol SUD in adolescence ($OR_{(0)} = 4.33/OR_{(1)} = 10.93$). Other adolescent characteristics that were significantly associated with ongoing and lifetime nicotine dependence at mean age 41 included number of antisocial behaviors, having dropped out of school, parental SUD, parental antisocial personality disorder as well as clinical ratings of hyperactivity and impulsivity (Table 4).

In contrast to another report of children followed longitudinally at age 21 (Pingault et al. 2013), we did not detect a significant association between clinician ratings of inattention severity and nicotine dependence in adulthood ($OR_{(0)} = 1.29, p = 0.06/OR_{(1)} = 1.21, p = 0.11$). Still, the significant associations of nicotine dependence at age 41 with hyperactivity, impulsivity, antisocial behaviors, having dropped out of school, parental SUD, parental antisocial personality disorder and alcohol/non-alcohol SUD are consistent with the finding, in this cohort, that dysfunctions that

children with ADHD experience throughout life, well into adulthood, originated during adolescence (Klein et al. 2012).

We did not observe a significant relationship between parental antisocial personality disorder (APD) and ongoing nicotine dependence in their adult offspring. The low prevalence of parental APD ($n = 15$) is likely to have limited the detection of a relationship, should it exist. Although the rate of non-alcohol SUD in parents of the ongoing nicotine dependent group was almost twice that in the non-dependent group (31 vs. 17%, respectively), the difference only reached the level of a trend ($p = 0.10$). Here again, a relatively low rate of parental antisocial disorder may have been a limiting factor. These two correlates were statistically significantly related to nicotine dependence when lifetime diagnoses were evaluated (OR's 4.42 and 3.58, respectively).

Although significant, the magnitude of the associations we observed was far from strong, as reflected in moderate odds ratios in adolescence; the same holds true for other studies that report significant predictors (Elkins et al. 2007; Pingault et al. 2013).

The main limitation of the study is the moderate sample size, diminished by total attrition over 33 years of 35%. However, as previously reported, there were minor differences between those retained over four waves of data collection and those lost to follow-up (Klein et al. 2012; Mannuzza et al. 2011; Ramos Olazagasti et al. 2013), so it is doubtful that attrition affected our positive results. Nevertheless, our inability to detect robust predictors in childhood beyond a rating of immaturity may reflect insufficient statistical power. We do not report on other SUD, as overall rates at age 41 were modest (14%) (Klein et al. 2012). We failed to assess parental tobacco use, which has been identified as a risk factor for nicotine dependence in adolescent offspring. There may be concern that the study sample, recruited in the 1970's, does not represent current standards for the diagnosis of ADHD. As noted elsewhere (Klein et al. 2012), the children's clinical presentation conforms closely to DSM-IV ADHD, combined type (e.g., they had pervasive impairing inattention and hyperactivity/impulsivity, a childhood onset, and ADHD was the salient clinical presentation). In some epidemiological studies, though not all, male sex is associated with nicotine dependence (Karp et al. 2005). Because our study is limited to Caucasian males who were raised in the 1970's, inference about other groups and cohorts may not be valid.

Conclusion

In a sample of white, middle-class boys with combined type ADHD, followed from mean ages 8–41, we failed to find specific childhood features that suggest elevated risk for nicotine dependence in adulthood. Unexpectedly,

children rated by psychiatrists as being immature were less likely to have a diagnosis of ongoing nicotine dependence in adulthood. In contrast, several characteristics in adolescence were significantly associated with nicotine dependence more than 20 years later; these included level of impulsivity and hyperactivity, antisocial behaviors, having dropped out of school, parental SUD, parental antisocial personality disorder and alcohol and non-alcohol SUD. These results reinforce the conclusion that many of the negative lifelong sequelae associated with ADHD, including nicotine dependence, originate in adolescence.

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Compliance with ethical standards

Conflict of interest None of the authors have any financial interest in relation to this study or its results.

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