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Predicting adolescent alcohol and other drug problems using electronic health records data

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ABSTRACT

Importance: Alcohol and other drug (AOD) use problems may cause significant burden on affected adolescents and their families, yet treatment providers often do not identify these problems early enough.
Objective: To develop, and internally and externally validate a multivariable prediction model of adolescent AOD problems using child- and maternal-level predictors before age 12, and child-level predictors between ages 12 to 18, as recorded in the electronic health records (EHR).
Design: A retrospective cohort study conducted time-to-event analyses using Cox proportional hazards models.
Setting and participants: 41,172 children born between 1997 and 2000 at four health plans (Kaiser Permanente Hawaii, KPHI; Kaiser Permanente Northern California, KPNC; Geisinger Clinic, GC; and Henry Ford Health System, HFHS) who had continuous membership since birth and linkable maternal records in the health plan.
Outcomes: AOD use problems between ages 12 to 18, defined as either: 1) having a contact with the AOD treatment program or 2) receiving a non-tobacco AOD diagnosis in an inpatient or outpatient encounter.
Exposures: Candidate predictor variables include demographics, socioeconomic status, and clinical diagnoses of the children and the mothers.
Results: Overall, 1400 (3.4%) adolescents had an AOD disorder between ages 12 to 18; the median follow-up time post–age 12 was 5.3 years. The research team developed two final prediction models: a "baseline" model of 10 child-level and 7 maternal-level predictors before age 12, and a more comprehensive "time-varying" model, which incorporated child risk factors after age 12 as time-varying covariates in addition to the baseline model predictors. Model performance evaluation showed good discrimination performance of the models, with the concordance index improved for the time-varying model, especially for prediction of AOD events in late adolescence.
Conclusions and relevance: This study identified a number of child and maternal characteristics and diagnoses routinely available in EHR data as predictive of risk for developing AOD problems in adolescence. Further, we found that risk of developing problems varies significantly by the timing and persistence of the risk factors. Findings may have potential clinical implications for prevention and identification of adolescent AOD problems, but more research is needed, especially across additional health systems.

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; AOD, Alcohol and Other Drug; DMDD, Disruptive Mood Dysregulation Disorder; EHR, Electronic Health Record; GC, Geisinger Clinic; HFHS, Henry Ford Health System; IBD, Inflammatory Bowel Disease; IBS, Irritable Bowel Syndrome; IPV, Intimate Partner Violence; KPHI, Kaiser Permanente Hawaii; KPNC, Kaiser Permanente Northern California; OCD, Obsessive Compulsive Disorder; PH, Proportional Hazards; SES, Socioeconomic Status.

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1. Introduction

Adolescent alcohol or other drug (AOD) use has been called "America's #1 Public Health Problem" (The National Center on Addiction and Substance Abuse (CASA) at Columbia University, 2009 [data file]). Adolescent AOD is associated with mortality and morbidity, including suicide, homicide, accidents and injuries, assaults, violence, victimization, sexual risk-taking and sexually transmitted infections, pregnancy, medical and mental health comorbidities, and other problems (Ammon et al., 2005; Berenson et al., 2001; Groth & Morrison-Beedy, 2011; Mertens et al., 2007; Oesterle et al., 2004; Reid et al., 2000; Sterling et al., 2004; Sterling & Weisner, 2005). Research has demonstrated the deleterious effects of AODs on the developing brain (Bava & Tapert, 2010; Squeglia et al., 2009; Windle et al., 2008), including potentially irreparable neurocognitive damage (Brown et al., 2000; Jacobus et al., 2013; Logue et al., 2014; Moss et al., 1994; Weigard et al., 2014; Zeigler et al., 2005). Adult AOD problems frequently begin in adolescence, and are associated with early initiation (Hingson et al., 2006a, 2006b). While adolescent AOD use has declined overall, drinking and drug use (especially marijuana and prescription opioids) are still highly prevalent, as are unhealthy practices like binge drinking, even among young adolescents (Johnston et al., 2014). Adolescent AOD is also costly; underage drinking alone in the United States costs upwards of $60 billion annually (Miller et al., 2006). Prevention and early intervention can make a critical difference to adolescent health (Blum, 1987; Brindis et al., 2002; Shrier et al., 2003).

Currently, clinicians' ability to predict who is most likely to develop AOD problems is poor, limited to anecdotal evidence and best-guesses, which research shows are often inaccurate (Wilson et al., 2004). Evidence supports the effectiveness of screening and early intervention, but those practices focus on current behaviors, not factors that might predict future problems. Heretofore, data-driven predictive models have been lacking, but such models, if robust and generalizable, could help clinicians to identify youth at higher risk for developing problems.

Health care providers have increasingly used predictive modeling (Linnen et al., 2019; O'Brien et al., 2020; Vranas et al., 2017) to leverage patient data from electronic health records (EHR)—now nearly ubiquitous in U.S. health care settings (Office of the National Coordinator for Health Information Technology, 2019)—for a range of health problems, from lung cancer prognosis (Kourou et al., 2015; Yu et al., 2016) to identifying risk for HIV (Krakower et al., 2019; Marcus et al., 2019). Providers have also used predictive modeling to predict psychiatric problems, notably suicidal behavior (Belsher et al., 2019; Walsh et al., 2017). However, to our knowledge, predictive modeling has not been used to identify adolescents at risk of developing AOD problems.

We aimed to develop a model predicting AOD problems between ages 12 and 18, conducting time-to-event analysis of data from a mother-child birth cohort across four health systems, using child- and maternal-related predictors before age 12, and child predictors between ages 12 and 18.

2. Methods

2.1. Study population

This observational, EHR-based retrospective cohort study identified a birth cohort of live adolescents, born between 1997 and 2000 in four health plans (Kaiser Permanente Hawaii, KPHI; Kaiser Permanente Northern California, KPNC; Geisinger Clinic, GC; and Henry Ford Health System, HFHS), with continuous membership coverage since birth, allowing a 12-month gap. The health plans' EHR linked adolescents to their mothers' medical record. If the EHR linked more than one child to a mother, the study team selected the oldest child.

2.2. Measures

The **outcome** of interest was development of an AOD problem during adolescence, defined as either: 1) having a contact with an AOD treatment program; or 2) receiving a nontobacco AOD diagnosis in inpatient or outpatient encounter during ages 12–18. The study calculated time to development of AOD problem as number of months from age 12 to first date of an AOD problem documented in the EHR. Three of the four sites offer full-service addiction treatment; one refers members to outside organizations for addiction services. The study confirmed AOD problems and treatment referrals documented at the latter site through manual review of clinical notes because addiction treatment utilization data from outside providers are not captured as structured data in that site's EHR. The study censored adolescents without an AOD problem during the study follow-up at either age 18 or at end of the study (December 31, 2015).

Using data extracted from the EHRs, we examined two sets of **potential predictor variables**—child-level and maternal-level—based on current literature (Alvarez-Aguirre et al., 2014; Bosque-Prous et al., 2017; Bushnell et al., 2019; Butwicka et al., 2017; Chen et al., 2012; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Fife & Forste, 2016; Goldstein et al., 2013; Groenman et al., 2017; Haller & Chassin, 2014; Howard et al., 2019; Keeley et al., 2015; Kelly et al., 2018; Lanza et al., 2015; Merikangas & McClair, 2012; Mertens et al., 2007; Schiff et al., 2014; Schinke et al., 2009; Stralin & Hetta, 2019) and input from developmental pediatricians, and psychiatrists and psychologists with expertise in child and adolescent development, from within and outside of the health systems. For **child-level** variables, we extracted sociodemographic data on birth-year, gender, race/ethnicity, insurance, and geocoded census data for neighborhood median household income and education. The study used ever Medicaid insured, low neighborhood median household income, and education level as proxy indicators for SES. Using data of ICD-9 and ICD-10 codes extracted from the EHR, we identified medical and psychiatric diagnoses by age 12 and between age 12 and 18, including attention deficit hyperactivity disorder (ADHD), anxiety/panic disorders, autism, bed wetting, bipolar disorders, communication disorders, conduct disorders, depression, development delay, development disorders, disruptive mood dysregulation disorder (DMDD), early puberty, eating disorders, gender dysphoria, headache, inflammatory bowel disease or irritable bowel syndrome (IBD/IBS), injury/poisoning, intellectual disabilities, intimate partner violence (IPV), learning disorders, migraine, motor disorders, obesity, obsessive compulsive disorder (OCD), oppositional defiant disorder, personality disorders, schizophrenia/psychotic disorders, self-harm, sleep disorders, somatic symptoms/disorders, and trauma/stress related disorders. The study obtained smoking status by age 12 from screening data at medical visits as recorded in EHR.

For **maternal-level** variables, we calculated age at birth using child's and mother's date of birth. We identified medical, AOD, and psychiatric comorbidities from 1 year prior to pregnancy to child's 12th birthdate based on EHR diagnoses using ICD-9 and ICD-10 codes. We examined AOD comorbidities by substance type, and psychiatric disorders including anxiety/panic disorders, bipolar disorders, eating disorders, injury/poisoning, IPV, major depression, non-major depression disorders, OCD, schizophrenia/psychotic disorders, and other psychiatric conditions. We obtained smoking status during the same time period from EHR screening data recorded at medical visits.

2.3. Further exclusion criteria

Thirty-six (N = 35 for KPNC and 1 for HFHS) of the 41,353 children had a recorded AOD problem before age 12 and the study team excluded them. In addition, small proportions (<1% across the 4 sites) of the cohort had missing data for any predictor. We included only those with non-missingness for all predictors in the analyses (N = 36,524 for KPNC, 2681 for KPHI, 1732 for HFHS, and 235 for GC).

2.4. Statistical analyses

2.4.1. Model development

Using KPNC data, we fit Cox proportional hazards (PH) models with time to development of an AOD problem between ages 12 and 18 as the outcome. We developed two sets of prediction models. The ***baseline model*** considered only child- and maternal-level predictors up to child's 12th birthdate. We followed the model selection approach suggested by Collett (2015), which involved 4 steps: 1) fit a univariate model for each predictor variable, and identify the predictors significant at level p = 0.1; 2) fit a multivariable model with all significant predictor variables identified in step 1, and use backward selection to eliminate nonsignificant variables at level p = 0.05; 3) start with final step 2 model, consider each of the nonsignificant variables in step 1 using forward selection, with significance level p = 0.05; and 4) do final pruning of the main-effects model using stepwise selection with significance level p = 0.05.

We next developed the ***time-varying model,*** extending the baseline model by adding 16 child's medical and psychiatric comorbidities between ages 12 and 18 as time-varying predictors: ADHD, anxiety/panic disorders, bipolar disorders, conduct disorders, depression, eating disorders, headache, injury/poisoning, IPV, migraine, OCD, oppositional defiant disorder, schizophrenia/psychotic disorders, sleep disorders, trauma/stress related disorders, and self-harm. The study team selected the 16 comorbidities based on results from the bivariate Cox PH models. To evaluate the effects of the presence and timing of the condition, for each condition, we created and examined 3 binary indicators: 1) receiving a diagnosis before age 12; 2) receiving a diagnosis after age 12; and 3) receiving a recent diagnosis in the past 3 months. We fit 16 multivariable time-varying models to examine each condition separately, then fit a final combined time-varying model to examine them jointly.

2.4.2. Model performance

We evaluated model discrimination using the concordance index for final baseline and final time-varying models. We randomly divided KPNC data into a model development dataset (2/3) and model validation dataset (1/3); the proportion with AOD outcome was approximately equal in both. We conducted internal validation using the KPNC validation dataset. The study team evaluated external validation of the final models using the combined dataset from KPHI, GC and HFHS, and the dataset from each site separately.

We conducted all analyses using SAS 9.4 and R3.5.0.

3. Results

Overall, 1400 (3.4%) adolescents had an AOD problem documented in their EHR between ages 12 and 18. The EHR followed adolescents from age 12 to age 18, with a median time post-age 12 of 5.3 years.

Bivariate Cox PH models among KPNC adolescents found that older age, lower SES, and Hispanic ethnicity were associated with higher risk, while female gender and Asian race were associated with lower risk of developing an AOD problem between 12 and 18. Having a diagnosis before age 12 of ADHD, anxiety/panic disorders, bed wetting, conduct disorders, depression, DMDD, eating disorders, headache, IBD/IBS, injury/poisoning, IPV, learning disabilities, migraine, OCD, oppositional defiant disorders, personality disorders, sleep disorders, self-harm, and trauma or stress related disorders were associated with higher risk of AOD problems between 12 and 18. Having an autism diagnosis before age 12 was associated with lower risk of AOD problems between 12 and 18. Maternal diagnoses of chronic pain, and AOD or psychiatric disorders prior to child's 12th birthdate were all associated with increased risk of AOD use problems of the child (not shown).

3.1. Baseline model of child- and maternal-level predictors up to child's 12th birthdate

The final baseline model included 17 child- and maternal-level predictors up to child's 12th birthdate (Table 1). After adjusting for birth year, race/ethnicity, and gender, having a diagnosis of ADHD, conduct disorder, headache, injury/poisoning, oppositional defiant disorder, and trauma or stress related disorders before age 12 were all associated with increased risk of AOD problems between ages 12 and 18. Among maternal factors, diagnoses of alcohol use disorder, cannabis use disorder, other drug use disorders, multiple drug use disorders, tobacco use disorder, and both major and nonmajor depression were all associated with increased risk of child AOD problems between 12 and 18.

3.2. Time-varying models with child's medical and psychiatric comorbidities between ages 12 and 18

We next examined effects of 16 medical and psychiatric comorbidities occurring in adolescents between ages 12 and 18 as time-varying covariates in multivariable Cox PH models. For each predictor, we fit a model including 3 binary indicators for either receiving a diagnosis for the condition before age 12, after age 12, or in the past 3 months, and compared the relative hazards for adolescent AOD problems across groups that are classified by presence and timing of having a condition. Table 2 illustrates the groups of comparison. For descriptive purposes, the study team characterized the resulting six groups as: 1) children without the condition up to end of the study (reference group, hazard = 1); 2) the "early" group, identified with the condition before age 12 but no longer having the diagnosis noted after age 12; 3) the "early persistent" group, with the diagnosis noted before and after age 12, but with no diagnosis noted in the past 3 months; 4) the "later" group, with the

Table 1
Final baseline model of child- and maternal-level predictors before child's 12th birthdate predicting adolescent AOD problems.

	aHR (95% CI)
Child-level predictors	
Race/ethnicity (reference = White)	
Asian	**0.49 (0.40, 0.60)**
Black	0.99 (0.83, 1.18)
Hispanic	**1.17 (1.03, 1.34)**
Hawaiian, or Pacific Islander	1.44 (0.83, 2.50)
Other	0.71 (0.49, 1.03)
Birth year (reference = 2000)	
1997	**1.64 (1.25, 2.15)**
1998	**1.46 (1.11, 1.92)**
1999	1.28 (0.97, 1.70)
Female (reference = male)	**0.89 (0.79, 0.99)**
Medical and psychiatric conditions (reference = no diagnosis)	
ADHD	**1.32 (1.10, 1.58)**
Autism	**0.34 (0.19, 0.62)**
Conduct disorders	**1.48 (1.15, 1.90)**
Headache	**1.35 (1.17, 1.56)**
Injury/poisoning	**1.21 (1.05, 1.41)**
Oppositional defiant disorders	**1.95 (1.47, 2.58)**
Trauma/stress related disorders	**1.57 (1.33, 1.86)**
Maternal-level predictors	
Substance use disorders (reference = No diagnosis)	
Alcohol use disorders	**1.33 (1.07, 1.66)**
Cannabis use disorders	**1.39 (1.06, 1.83)**
Multiple drug use disorders	**2.59 (1.05, 6.38)**
Other drug use disorders	**1.62 (1.17, 2.23)**
Tobacco use disorders	**1.36 (1.18, 1.57)**
Psychiatric conditions (reference = No diagnosis)	
MDD	**1.45 (1.26, 1.68)**
Non-MDD depression disorders	**1.41 (1.22, 1.64)**

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; aHR, Adjusted Hazard Ratio; AOD, Alcohol and Other Drug; CI, Confidence Intervals; MDD, Major Depression Disorders.
Bold values indicates statistically significance at P<0.05.

Table 2
Schema for comparing hazards between groups by presence and timing of a condition.

Group	Having a diagnosis of the condition before age 12	Having a diagnosis of the condition after age 12	Having a diagnosis of the condition in past 3 months	Hazards
None	No	No	No	1.0 (reference)
Early	Yes	No	No	
Early persistent	Yes	Yes	No	
Late	No	Yes	No	
Early persistent & recent	Yes	Yes	Yes	
Late & recent	No	Yes	Yes	

condition noted after age 12, but with no diagnosis in the past 3 months; 5) the "early persistent & recent" group, with the diagnosis noted before and after age 12, as well as in the past 3 months; and 6) the "later and recent" group of children identified with the condition after age 12 and noted in the past 3 months.

Results from each of the 16 individual, time-varying Cox PH models suggest that for most conditions, when compared to children without the condition, the "early" group had hazards either not significantly different or slightly lower, and the "early persistent" group had higher hazards. Across conditions, having a diagnosis (especially a recent diagnosis) after age 12 was a stronger risk predictor. For self-harm and trauma or stress-related disorders, the "early" group did have a significantly higher relative risk compared to the reference group, suggesting that having the condition even before age 12 was still associated with higher risk (Table 3). Results from the final, combined time-varying model suggest that having an autism or self-harm diagnosis before age 12 were associated with lower and higher risks of AOD use problems between ages 12 and 18, respectively (Table 4). Having a diagnosis of ADHD, depression, eating disorders, or oppositional defiant disorders after age 12 was associated with higher risk of adolescent AOD problems. Having recent diagnoses of depression, bipolar disorder, or headache also conferred significant risk. For trauma or stress-related disorders, having a diagnosis before or after age 12, or within the past 3 months, were all significant risk indicators.

3.3. Model performance

The concordance index for the baseline model was 0.67 (95% CI = 0.64–0.69). When conducting external validation of the baseline model using the combined non-KPNC datasets, we acquired the concordance index of 0.64 (95% CI = 0.59–0.70); but when validating on the KPHI dataset, we acquired a higher concordance index of 0.69 (95% CI = 0.64–0.75) (Table 5).

For internal and external validation of the final time-varying model, we computed the concordance index at each age from ages 12 to 17 (Table 5). Results suggest good discrimination performance, with the concordance index improved for prediction of AOD events in late adolescence.

4. Discussion

In this study, we employed machine learning approaches and rich child- and maternal-level EHR data from a diverse sample of more than 41,000 adolescents across four health systems to develop and validate two models predicting the development of AOD problems during adolescence, which has not been previously reported in the literature.

Through development of a model using exposures occurring before age 12, we found several child and maternal factors that raised or lowered the risk of developing an AOD problem. Girls, children of Asian or "other" ethnicity, and those with autism spectrum or developmental disorders had lower risk, and children who grew up in poorer neighborhoods, with lower average educational attainment, and those covered through Medicaid had higher risk of developing such problems. Several children's medical and mental health conditions occurring before age 12 conferred additional risk. Among them, ADHD, depression, bipolar disorder, trauma/stress disorders, oppositional defiant disorder, eating disorders, self-harm, and headache remained significant predictors of AOD problems between 12 and 18, after adjusting for other

Table 3
Comparisons of hazards between groups by presence and timing of medical and psychiatric condition.

Timing	ADHD	Anxiety/panic disorders	Bipolar disorders	Conduct disorders	Depression	Eating disorders
None	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Early	**0.64 (0.49, 0.83)**	0.97 (0.85, 1.11)	0.82 (0.62, 1.09)	1.17 (0.88, 1.56)	0.69 (0.45, 1.07)	1.05 (0.74, 1.50)
Early persistent	**1.46 (1.18, 1.82)**	**1.72 (1.37, 2.15)**	**2.76 (1.83, 4.15)**	**3.10 (2.22, 4.35)**	**2.15 (1.35, 3.43)**	**3.84 (2.23, 6.61)**
Early persistent recent	**2.76 (2.15, 3.55)**	**4.73 (3.71, 6.03)**	**8.26 (5.42, 12.61)**	**7.38 (4.41, 12.35)**	**7.83 (4.93, 12.43)**	**10.61 (6.13, 18.37)**
Late	**2.29 (1.78, 2.96)**	**1.77 (1.46, 2.15)**	**3.36 (2.49, 4.53)**	**2.65 (1.99, 3.53)**	**3.12 (2.61, 3.72)**	**3.65 (2.42, 5.51)**
Late recent	**4.33 (3.34, 5.61)**	**4.88 (3.97, 5.99)**	**10.07 (7.18, 14.13)**	**6.30 (3.86, 10.28)**	**11.32 (9.60, 13.36)**	**10.08 (6.65, 15.29)**

Timing	Headache	Injury/poisoning	Intimate partner violence	Migraine	OCD	Oppositional defiant disorders
None	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Early	**1.24 (1.07, 1.44)**	1.15 (0.99, 1.34)	1.08 (0.96, 1.22)	1.06 (0.79, 1.41)	1.19 (0.83, 1.72)	0.94 (0.65, 1.36)
Early persistent	**1.89 (1.54, 2.31)**	**1.99 (1.65, 2.41)**	**1.53 (1.13, 2.08)**	**1.53 (1.12, 2.10)**	1.68 (0.91, 3.10)	**3.96 (2.79, 5.62)**
Early persistent recent	**4.49 (3.23, 6.25)**	**2.95 (2.35, 3.71)**	**3.36 (2.16, 5.23)**	**3.07 (2.00, 4.72)**	**2.42 (1.07, 5.50)**	**11.48 (7.68, 17.17)**
Late	**1.52 (1.29, 1.79)**	**1.73 (1.51, 1.97)**	**1.42 (1.07, 1.87)**	**1.45 (1.14, 1.84)**	1.41 (0.86, 2.30)	**4.20 (3.12, 5.66)**
Late recent	**3.63 (2.67, 4.91)**	**2.56 (2.14, 3.07)**	**3.11 (2.04, 4.73)**	**2.90 (1.96, 4.31)**	2.03 (0.96, 4.30)	**12.19 (8.28, 17.95)**

Timing	Schizo/psychotic disorders	Self-harm	Sleep disorders	Trauma/stress related disorders
None	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Early	0.86 (0.52, 1.41)	**6.70 (1.80, 25.02)**	1.05 (0.83, 1.33)	**1.27 (1.06, 1.51)**
Early persistent	**3.66 (1.77, 7.56)**	**35.08 (9.20, 133.83)**	**2.26 (1.66, 3.07)**	**2.84 (2.30, 3.51)**
Early persistent recent	**8.22 (3.20, 21.11)**	**102.93 (26.07, 406.40)**	**3.99 (2.41, 6.60)**	**8.67 (6.54, 11.49)**
Late	**4.27 (2.52, 7.24)**	**5.23 (3.79, 7.22)**	**2.15 (1.66, 2.79)**	**2.24 (1.87, 2.68)**
Late recent	**9.59 (4.34, 21.18)**	**15.35 (9.40, 25.09)**	**3.79 (2.36, 6.11)**	**6.85 (5.36, 8.76)**

Note: For each condition, adjusted relative hazards and 95% confidence intervals across groups were estimated from a separate model adjusting for all predictors that were included in the final baseline model. Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; OCD, Obsessive Compulsive Disorder.
Bold values indicates statistically significance at $P<0.05$.

Table 4
Final time-varying model with child- and maternal-level predictors before child's 12th birthdate, and child-level predictors between ages 12 and 18, predicting adolescent AOD problems.

		aHR (95% CI)
Child-level predictors		
Race/ethnicity (reference = White)		
Asian		**0.56 (0.45, 0.69)**
Black		1.03 (0.86, 1.24)
Hispanic		**1.23 (1.07, 1.40)**
Hawaiian, or Pacific Islander		1.34 (0.75, 2.38)
Other		0.71 (0.49, 1.04)
Birth year (reference = 2000)		
1997		**3.93 (3.03, 5.10)**
1998		**2.70 (2.07, 3.52)**
1999		**1.75 (1.33, 2.32)**
Female (reference = male)		0.72 (0.64, 0.81)
Medical and psychiatric conditions (reference = no diagnosis)		
ADHD	Diagnosis before age 12	0.85 (0.67, 1.08)
	Diagnosis after age 12	**1.71 (1.34, 2.17)**
	Diagnosis in past 3 months	0.85 (0.63, 1.14)
Anxiety/panic disorders	Diagnosis before age 12	1.01 (0.88, 1.16)
	Diagnosis after age 12	0.91 (0.73, 1.13)
	Diagnosis in past 3 months	1.11 (0.84, 1.46)
Autism	**Diagnosis before age 12**	**0.41 (0.23, 0.75)**
Bipolar disorders	Diagnosis before age 12	0.73 (0.53, 1.01)
	Diagnosis after age 12	1.18 (0.87, 1.61)
	Diagnosis in past 3 months	**1.77 (1.16, 2.68)**
Conduct disorders	Diagnosis before age 12	1.14 (0.85, 1.54)
	Diagnosis after age 12	1.17 (0.85, 1.62)
	Diagnosis in past 3 months	1.11 (0.65, 1.88)
Depression	Diagnosis before age 12	0.72 (0.45, 1.13)
	Diagnosis after age 12	**2.23 (1.82, 2.74)**
	Diagnosis in past 3 months	**2.80 (2.19, 3.58)**
Eating disorders	Diagnosis before age 12	0.88 (0.59, 1.30)
	Diagnosis after age 12	**1.99 (1.32, 3.02)**
	Diagnosis in past 3 months	1.28 (0.72, 2.25)
Headache	Diagnosis before age 12	1.13 (0.97, 1.32)
	Diagnosis after age 12	1.15 (0.97, 1.37)
	Diagnosis in past 3 months	**1.76 (1.26, 2.48)**
Intimate partner violence	Diagnosis before age 12	1.02 (0.90, 1.16)
	Diagnosis after age 12	0.88 (0.66, 1.16)
	Diagnosis in past 3 months	1.40 (0.85, 2.29)
Injury/poisoning	Diagnosis before age 12	1.05 (0.79, 1.40)
	Diagnosis after age 12	1.12 (0.87, 1.44)
	Diagnosis in past 3 months	1.11 (0.71, 1.74)
Migraine	Diagnosis before age 12	1.05 (0.79, 1.40)
	Diagnosis after age 12	1.12 (0.87, 1.44)
	Diagnosis in past 3 months	1.11 (0.71, 1.74)
OCD	Diagnosis before age 12	1.07 (0.70, 1.62)
	Diagnosis after age 12	0.66 (0.37, 1.17)
	Diagnosis in past 3 months	0.79 (0.32, 1.99)
Oppositional defiant disorders	Diagnosis before age 12	0.97 (0.68, 1.39)
	Diagnosis after age 12	**2.19 (1.60, 2.99)**
	Diagnosis in past 3 months	1.42 (0.92, 2.19)
Schizo/psychotic disorders	Diagnosis before age 12	1.14 (0.66, 1.95)
	Diagnosis after age 12	0.93 (0.52, 1.66)
	Diagnosis in past 3 months	1.02 (0.38, 2.69)
Self-harm	**Diagnosis before age 12**	**4.61 (1.62, 13.10)**
	Diagnosis after age 12	1.35 (0.94, 1.94)
	Diagnosis in past 3 months	1.02 (0.55, 1.91)
Sleep disorders	Diagnosis before age 12	1.01 (0.80, 1.28)
	Diagnosis after age 12	1.13 (0.86, 1.50)
	Diagnosis in past 3 months	0.91 (0.52, 1.60)
Trauma/stress related disorders	**Diagnosis before age 12**	**1.23 (1.03, 1.47)**
	Diagnosis after age 12	**1.21 (1.00, 1.48)**
	Diagnosis in past 3 months	**2.07 (1.55, 2.76)**
Maternal-level predictors		
Substance use disorders (reference = No diagnosis)		
Alcohol use disorders		**1.29 (1.01, 1.65)**
Cannabis use disorders		**1.34 (1.01, 1.79)**
Multiple drug use disorders		**2.91 (1.29, 6.59)**
Other drug use disorders		**1.56 (1.10, 2.20)**
Tobacco use disorders		**1.28 (1.11, 1.48)**
Psychiatric conditions (reference = No diagnosis)		
Major depression		**1.68 (1.06, 2.68)**
Non-major depression disorders		**1.80 (1.14, 2.84)**

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; aHR, Adjusted Hazard Ratio; AOD, Alcohol and Other Drug; CI, Confidence Intervals; MDD, Major Depression Disorders; OCD, Obsessive Compulsive Disorder.
Bold values indicates statistically significance at $P<0.05$.

Table 5
Predictive performance of model discrimination, final multivariable baseline model and time-varying model.

	Internal validation			External validation					
	KPNC			GC, HFHS, and KPHI combined			KPHI only		
	N	C-index	95% CI	N	C-index	95% CI	N	C-index	95% CI
Baseline model									
Age 12	12,172	0.67	(0.64, 0.69)	4648	0.64	(0.59, 0.70)	2681	0.69	(0.64, 0.75)
Time-varying model									
Age 12	12,172	0.66	(0.63, 0.68)	4648	0.67	(0.62, 0.71)	2681	0.69	(0.64, 0.74)
Age 13	12,165	0.68	(0.65, 0.70)	4646	0.68	(0.64, 0.73)	2680	0.70	(0.65, 0.76)
Age 14	12,130	0.71	(0.68, 0.73)	4628	0.70	(0.66, 0.75)	2667	0.74	(0.68, 0.79)
Age 15	12,052	0.74	(0.71, 0.77)	4604	0.73	(0.68, 0.79)	2647	0.78	(0.73, 0.83)
Age 16	11,938	0.78	(0.75, 0.81)	4564	0.70	(0.63, 0.77)	2620	0.81	(0.74, 0.87)
Age 17	11,846	0.81	(0.77, 0.85)	4528	0.78	(0.69, 0.86)	2595	0.84	(0.73, 0.94)

Abbreviations: AOD, Alcohol and Other Drug; C-index, Concordance index; CI, Confidence Intervals; GC, Geisinger Clinic; HFHS, Henry Ford Health System; KPHI, Kaiser Permanente Hawaii; KPNC, Kaiser Permanente Northern California.

covariates. Our findings echo those of other studies that found childhood mental health comorbidities to be associated with AOD use problems (Abram, 2016; Conway et al., 2016).

We also found that the presence of several maternal-level mental health and medical conditions during childhood predicted adolescent AOD problems, including both major and nonmajor depressive disorders, alcohol, cannabis, other drug, multiple drug, and tobacco use disorders. Research has found similar associations between parental mental health problems and children's AOD use (Axelson et al., 2015; Batten et al., 2012; Buu et al., 2009), and our study reflects the findings of other studies on the intergenerational nature of AOD problems, whether due to heredity, environmental mechanisms, or both (Hines et al., 2015).

In the final model, which included exposures occurring from age 12 onward to account for critical influences during adolescence, a complex picture emerged related to the timing of exposures. Some exposures before age 12 remained significant predictors, including autism spectrum disorders, which continued to confer lower risk; and self-harm, which continued to confer greater risk. For several conditions, however, only diagnoses occurring after age 12 (ADHD, eating disorders, and oppositional defiant disorder) or diagnoses in the 3 months prior to identification of the AOD problem (bipolar disorder and headache) were associated with higher risk. Depression occurring from age 12 on, including in the 3 months prior to AOD problem identification, conferred higher risk. Among all the child-level conditions, only trauma or stress-related diagnoses, occurring at *any* point, were associated with higher risk. Girls and Asian adolescents remained at lower risk even when accounting for all other factors.

Examining each condition separately, controlling for other significant factors in the baseline model, we saw a chronological pattern emerge, with implications for magnitude of risk of future AOD problems: while early exposure alone often did not increase risk, risk tended to increase with the recency of exposure, with ongoing, persistent conditions (particularly those beginning in childhood) being strong predictors in many cases. This approach—evaluating the impact of the timing of exposures—is unique in the literature on pediatric AOD use risk.

That the risk conferred by child-level factors varies by the timing of diagnoses could be interpreted as hopeful: it may be that many childhood mental health problems, if resolved prior to adolescence (either on their own or through successful treatment), do not necessarily increase AOD risk, which families and clinicians may find reassuring. These results could also provide evidence-based rationale for the implementation of early behavioral health interventions for children, to diminish future risk.

However, for certain conditions (headache, trauma/stress-related disorders, and self-harm), an early diagnosis alone predicted higher risk of AOD problems. Clinicians should be aware of the particular vulnerability of patients with these conditions, especially self-harm, which raised risk substantially whenever it occurred. Understanding the magnitude of risk for subsequent AOD problems could educate parents and clinicians on the need to create supportive "scaffolding" for the most vulnerable children and teens.

The role of maternal-level AOD use and mental health conditions in increasing the risk of adolescent AOD problems is noteworthy. The evidence of these models further supports the long-recognized association between family and adolescent AOD problems. While the study could not disentangle genetic, epigenetic, and environmental effects, its findings reinforce that adolescent AOD problems often reflect family AOD use, and children of parents with AOD problems are particularly vulnerable themselves. Similarly, children of mothers with both major and nonmajor depression were at significantly higher risk of developing AOD problems, even when taking into account other factors. The findings underscore the need for robust perinatal and early childhood screening and support interventions (e.g., systematic perinatal depression screening), and for parenting programs in pediatric primary care.

These models could inform development of targeted screening and assessment tools by translating complex EHR data into risk levels that are more useful for clinicians. For example, the findings could aid in creating evidence-based "red flags" in EHRs indicating the presence of risk factors, to remind pediatricians to screen especially vulnerable patients for AOD risk and conduct early anticipatory guidance. Findings could be helpful to families, if disseminated in digestible, easy-to-comprehend formats, providing additional information for weighing the role of risks and informing decisions about early intervention or treatment. The findings could also help youth-serving systems to target and tailor finite resources for screening and intervention by risk level.

4.1. Limitations

This study has several limitations. The study based determination of the outcome (AOD event) on having a contact with the AOD treatment program or receiving an AOD diagnosis, and thus we may not have identified adolescents with less severe AOD problems. As a result, the prevalence of the outcome was low, especially in early adolescence, which may explain the model's underperformance in predicting AOD problems in early adolescence. Prevalence rates of several potential predictor variables were also low, which precluded our including them in the final model. In addition, several important behavioral or risk factors that may be available in clinical progress notes were not available across all four health plans and thus we could not examine them in the current study. Lack of consistency in longitudinal EHR data (either within a health plan or across health plans) is a challenge in this type of research design, as quality and availability of the data may vary by factors at patient (e.g., patterns of utilization), provider (e.g., diagnostic behaviors) and system levels (e.g., differences in coding conventions over time or across health plans). This difference may result in restricted

generalizability of the study findings and underlines the importance of more research, including validating the predictive models to other large health systems nationally. We examined the EHR data of children born in four health systems and required continuous membership for both children and mothers; thus, their records were easily linkable. Unfortunately, fathers' records are not automatically linked to children's records and it was beyond the scope of this study to attempt to link fathers' and children's records. While both mothers' and fathers' clinical characteristics most certainly influence their children's health and well-being, research suggests a stronger relationship between maternal compared to paternal factors and child behavioral health problems (Cabrera et al., 2011; Kahn et al., 2004; Keeley et al., 2015; Schinke et al., 2009). Nevertheless, the relationship between paternal factors (or combined paternal and maternal factors) and child outcomes is very important to understand and warrants future research.

5. Conclusions

Historically, clinicians have lacked evidence-based ways to precisely target and tailor prevention, screening, and intervention efforts for children at greatest risk of AOD problems. Health and other service systems often face limited resources and must determine how to use scarce resources based on limited information. Accurate predictive models could focus resources on those at highest risk, permitting a wiser stewardship of finite funding. Our findings can add to the arsenals of clinical leaders and policy-makers as they address adolescent AOD use and its consequent harm to adolescent health.

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CRediT authorship contribution statement

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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