Forecasting Opioid Use Disorder at 25 Years of Age in 16-Year-Old Adolescents

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Objective To evaluate the accuracy of detecting 16-year-old male (n = 465) and female (n = 162) youths who subsequently manifest opioid use disorder (OUD) at 25 years of age. We hypothesized that the combined measures of 2 components of etiology, heritable risk, and substance use, accurately detect youths who develop OUD.

Study design Heritable risk was measured by the transmissible liability index (TLI). Severity of the prodrome presaging OUD was quantified by the revised Drug Use Screening Inventory containing the consumption frequency index (CFI) documenting substance use events during the past month and the overall problem density (OPD) score indicating co-occurring biopsychosocial problems. Diagnosis of OUD was formulated by a clinical committee based on results of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition in conjunction with medical and social history records.

Results Bivariate analysis shows that the TLI, CFI, and OPD scores at 16 years of age predict OUD at 25 years. Multivariate modeling indicates that the TLI combined with the CFI predict OUD with 86% accuracy (sensitivity = 87%; specificity = 62%). The TLI and CFI at 16 years of age mediate the association between parental substance use disorder and OUD in offspring at 25 years of age, indicating that these measures respectively evaluate risk and prodrome.

Conclusions These results demonstrate the feasibility of identifying youths requiring intervention to prevent OUD. *(J Pediatr 2020;225:207-13)*.

Over 11 000 000 Americans misused prescription opioids in 2017.[1] Prescription opioid use is especially concerning for adolescents considering that high school seniors using opioids prescribed by a physician have 33% increased risk of misuse 5 years later.[2] The observation that each year opioid use onset delayed after age 13 years lowers risk of misuse by 2%[3] underscores the importance of prevention directed at adolescents, especially considering that self-directed (ie, nonprescribed) consumption of opioids ranks second in prevalence after cannabis within the spectrum of illegal drugs.[4,5] Moreover, using Schedule I opioids, particularly heroin, is frequently preceded by consuming prescription opioids.[6,7]

The present longitudinal investigation examined the accuracy of forecasting opioid use disorder (OUD) manifest at 25 years of age based on measurement of 2 main etiologic components, heritable liability,[8] and substance use, at 16 years of age. Significantly, 16 years of age is the most frequent time of onset of opioid use[9] and 25 years of age is the midpoint within the period of peak OUD prevalence in the general population.[10] Considering that 30% of the population receiving treatment for hazardous opioid use are younger than 24 years of age[11] and remission rate is one-half other addictions,[12] demonstrating accurate prediction of OUD advances the opportunity to efficiently detect high risk youths so that prevention interventions can be expeditiously implemented.

Methods

Participants were recruited by the Center for Education and Drug Abuse Research, a National Institute on Drug Abuse-funded longitudinal study of substance use disorder etiology.[13] Men with either lifetime substance use disorder consequent to using an illegal drug (n = 334) or those who did not qualify for any adult-onset psychiatric disorder (n = 340), and had a 10- to 12-year-old biological son (n = 482) or daughter (n = 191), were identified using random digit telephone calls, advertisement, and public service announcements. In addition, approximately 25% of the men with substance use disorder were identified after discharge from addiction treatment facilities. Because prodrome severity indicated by substance use frequency cannot be meaningfully measured in 10- to 12-year-old youths owing to low incidence of consumption onset, the evaluation was deferred until

AUC	Area under the curve
CFI	Consumption frequency index
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUSI-R	Drug Use Screening Inventory-Revised
OPD	Overall problem density
OUD	Opioid use disorder
TLI	Transmissible liability index

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Supported by the National Institute on Drug Abuse (P50DA005605), Centers for Disease Control (R01CE00299601), and National Institute on Drug Abuse (UG1DA04944401). The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.07.025

the sample attained 16 years of age. Youths were disqualified from participating in the study if they had a chronic medical disorder requiring physician monitoring, physical disability, history of neurologic injury resulting in hospitalization, or an IQ below 80. Socioeconomic status of the boys (mean = 41.0, SD = 13.3) and girls (mean = 41.9, SD = 14.9) is middle class based on the Hollingshead 4-factor index.[14] IQ, evaluated by the WISC-III,[15] is in the average range in the boys (mean = 107.0, SD = 15.8) and girls (mean = 104.2, SD = 16.2). African-American boys and girls respectively constituted 23% and 33% of the sample.

Attrition between baseline (age 16 years) and outcome (age 25 years) assessments was 33% in boys and 17% in girls. The most frequent reasons for attrition were relocation (including military service and incarceration) and inability to contact the participant despite deploying a comprehensive tracking protocol. Notably, the attrited and retained segments of the male sample do not differ on the transmissible liability index (TLI), consumption frequency index (CFI), and overall problem density (OPD) predictor variables. The CFI score was, however, higher among girls who attrited. Rate of substance use disorder in parents, as shown in **Table I**, is not different between the attrited and retained segments of the sample. Overall, these comparisons indicate that male and female youths who participated in the outcome assessment are representative of the baseline sample as indicated by scores on the OUD predictors, IQ, socioeconomic status, rate of parental substance use disorder, and ethnicity. In the retained segment of the sample 6.4%, 25.1%, and 22.5% qualified for opioid, alcohol, or cannabis disorder.

Measures

Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised[16]. Diagnostic formulation of the parents and their children was conducted using the best estimate procedure.[17] This procedure takes into account the respondent's answers using an elaborated version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) to conform with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria in conjunction with pertinent information contained in medical and social services records. Diagnoses were formulated by a committee chaired by a psychiatrist certified in addiction psychiatry. The other members included another psychiatrist or a psychologist and Master-level clinical associates who conducted the Structured Clinical Interview for DSM-III-R. The DSM-IV taxonomy was employed for diagnosis of the parents and their children because this study began prior to advent of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Notably, diagnosis based on DSM-IV criteria has excellent correspondence with DSM-5.[18]

Parental Substance Use Disorder. Number of parents (0, 1, 2) with substance use disorder was recorded to measure magnitude of familial loading for this disorder in their children. This indicator of intergenerational risk has been shown in prior research to be heuristic for elucidating the risk for and developmental patterning to substance use disorder.[19,20] Number of affected parents was recorded in this study to confirm that magnitude of TLI score mediates the association between magnitude of child's familial loading for substance use disorder and their risk for OUD. Among the boys, 48.3%, 34.6%, and 17.1% had 0, 1, or 2 affected parents. The distribution was 51.8%, 29.6%, and 18.6% in the sample of girls.

TLI. Previous reports describe the theory[21] and methods[8,22] guiding development and validation of the TLI. Briefly, transmissible liability is the component of phenotypic variance that is correlated between generations via genetic and/or environmental influences. Because liability for substance use disorder is transmissible (as it has been shown to be significantly heritable), psychological and health behavior characteristics that discriminate children of affected and unaffected parents are indicators of children's own liability,[8] making it quantifiable on a continuous scale using item response theory methods.[22] Importantly, the genetic component of variance fully accounts for the correlation between the TLI score in 10- to 12-year-old children and their subsequent substance use disorder diagnosis.[23,24] Moreover, the TLI predicts substance use disorder better than parental diagnosis of this disorder.[25] The TLI version validated for 16-year-old youth with internal reliability exceeding 0.90,[26] was self-administered. This age-specific TLI contains 65 items that for the most part assess illegal activities (eg, "In the past 6 months, have you stolen or attempted to steal things worth between $5 and $50") and self-management in daily routines (eg, "I plan and organize my work in detail").

Drug Use Screening Inventory-Revised[27,28]. The self-administered Drug Use Screening Inventory-Revised (DUSI-R) measures severity of problems pertaining to (1) substance use, (2) mental health, (3) physical health, (4) behavior self-regulation, (5) school adjustment, (6) family functioning, (7) peer relationships, (8) social skills, (9) work adjustment, and (10) leisure/recreation activities. The OPD score is computed by dividing the number of items in which a problem is endorsed by the total number of items (n = 149) encompassing the 10 scales and then multiplying the resultant quotient by 100. The OPD score, thus, has a range of 0% to 100%. The mean OPD scores in the samples of boys and girls are 18.5% and 20.4%.

Convincing evidence demonstrates that liabilities to all substance use disorder categories share to large extent genetic and phenotypic variance.[22,29] Accordingly, opioid use is often concurrent with consumption of other addictive substances. Measuring prodrome severity, therefore, requires quantifying overall involvement with addictive substances. In this study, the number of alcohol and drug use events during the past 30-days was recorded by the DUSI-R's CFI. Consumption of 20 addictive substances was recorded in 5 categories to document past 30-day exposure: 0 (0 times), 1 (1-2 times), 2 (3-9 times), 3 (10-20 times), and 4 (more than 20 times). The category designations (0, 1, 2, 3, and 4) are summed across all substances to obtain the CFI. Expectedly, the 3 most frequently used substances were alcohol (29.6 %), tobacco (23.6 %), and cannabis (21.7 %). The mean CFI score is 1.86 in the sample of boys and 1.52 in the girls. The DUSI-R's Lie scale, consisting

Table I. Characteristics of the sample at 16 years of age who were retained or attrited at 25 years of age

	Male			Female		
	Retained (n = 305)	Attrited (n = 151)	Test statistics	Retained (n = 135)	Attrited (n = 27)	Test statistics
SUD in father (probands)	49%	56%	$\chi^2 = .06$, $P = .81$	41%	52%	$\chi^2 = .35$, $P = .55$
SUD in mother	20%	26%	$\chi^2 = .07$, $P = .79$	20%	39%	$\chi^2 = 2.66$, $P = .10$
IQ (mean, SD)	108.7 (15.3)	106.3 (16.5)	t = 2.61, $P = .01$	104.8 (17.2)	100.7 (14.4)	t = 2.43, $P = .02$
Family SES (mean, SD)	41.4 (13.2)	40.8 (13.6)	t = 1.50, $P = .13$	42.7 (14.7)	41.0 (16.1)	t = 1.60, $P = .14$
Ethnicity						
Euro-American	77%	78%	$\chi^2 = .98$, $P = .32$	67%	59%	$\chi^2 = .08$, $P = .78$
African American	23%	22%		33%	41%	
TTLI (z score)	.05 (1.01)	.12 (1.06)	t = −.57, $P = .56$	-.23 (.97)	.04 (.87)	t = −1.04, $P = .29$
CCFI*	1.86 (2.34)	2.16 (2.43)	t = −1.52, $P = .13$	1.52 (1.95)	2.50 (2.34)	t = −2.79, $P = .006$
OPD (%)†	18.52 (12.79)	16.28 (12.34)	t = 1.58, $P = .11$	20.38 (12.85)	21.99 (13.37)	t = −.48, $P = .63$

SES, socioeconomic status; *SUD*, substance use disorder.
*Consumption events in past month.
†Score ranges from 0-10.

of 10 items, assesses propensity to under-report problems. None of the participants were excluded from study based on the Lie scale score.

At baseline (age 16 years), only 6% of the sample reported lifetime opioid use, whereas 24% of the sample used opioids at least once by age 25 years. By age 25 years (outcome), OUD was present in 6.4% of the sample (6.2% male; 6.7% female); however, information was not available regarding whether the first opioid used was a medicine prescribed by a physician, was self-directed, or involved a Schedule I substance.

Procedure

After orientation to the laboratory, the parents and their children respectively signed the informed consent and assent forms approved by the University of Pittsburgh Institutional Review Board. Privacy was additionally assured by a *Certificate of Confidentiality* issued to the Center for Education and Drug Abuse Research by the National Institute on Drug Abuse to Center for Education and Drug Abuse Research. Next, the participants underwent a breath alcohol and urine drug screen to preclude possible biased responses consequent to substance-induced altered physiological state. The research protocol was administered individually in fixed order in a private sound-attenuated room. Upon completing the assessments, the data were reviewed by a clinical associate to ensure that all the questions were answered. Lastly, the participants were debriefed and compensated for their time and expenses.

Statistical Analyses

Analyses were conducted at the outset to confirm that the TLI and CFI/OPD are respectively valid measures of transmissible risk and OUD prodrome. Polyserial correlation evaluated the relationship between the participant's familial loading of substance use disorder (ie, number of affected parents) and TLI score. Point-biserial correlation estimated the association between TLI, CFI, and OPD scores and OUD.

Next, multisample path analysis was conducted to model the relationships between number of affected parents and their children's TLI, CFI, and OPD scores at 16 years of age and OUD at 25 years of age. Three models were compared. Model 1 assumed that all path (standardized partial regression) coefficients, means, and variances are equal between boys and girls. Model 2 assumed that only the path coefficients are equal. Model 3 assumed that all parameters are free. Path coefficients were estimated using Mplus (Muthén and Muthén, Los Angeles, California)[30] with weighted least squares with mean and variance correction designed for categorical and ordered data. Four indexes were computed to inform selection of the best model: (1) χ^2 goodness-of-fit index, (2) root mean square error of approximation, (3) comparative fit index, and (4) Tucker-Lewis index. Nonsignificant χ^2, root mean square error of approximation below 0.05, and comparative fit and Tucker-Lewis indexes close to 1 indicate good fit. Fit comparisons between the nested models (differing in that the parameters in the more general model are equated or absent from another model) are conducted using the difference of χ^2 values between the models. This statistic has an asymptotic χ^2 distribution with the degrees of freedoms equal to the difference between the degrees of freedom of the models. Mediation analyses were conducted employing the method described by Sobel[31] to ascertain whether TLI accounts for the association between number of affected parents and risk for OUD in their children. Accuracy of the TLI, CFI, and OPD scores for detecting youths who subsequently develop OUD was evaluated using multiple logistic regression analysis followed by receiver operating characteristic analysis documenting sensitivity (true positive rate), specificity (true negative rate), and overall accuracy. K-fold cross-validation, a resampling procedure used in machine learning, was employed to assess the predictive performance of the logistic model using area under the curve (AUC) for new cases to predict OUD. This predictive model thus can be generalized to new samples. It is a preferred method when there are not large enough number of observations in a sample. When AUC is estimated from the whole sample, it is usually overestimated because of overfitting. The k-fold cross-validation, by randomly dividing the data into k subsets (folds) to compute AUC for each fold, provides more accurate estimates, which in turn yield better predictive models. Then AUCs are averaged and an SE for the average AUC is generated by bootstrapping. In this paper, the data were divided into 5 folds. Although this number is acceptable,[32] a greater number of folds could not be specified because of the low prevalence of OUD in the sample.

Results

Bivariate Correlations

As can be seen in Table II, number of parents with substance use disorder is related to TLI score in 16-year-old boys and girls. The TLI score in turn correlates with OUD outcome in both sexes. The TLI score also correlates with CFI score in boys and girls which, in turn, is related to OUD. In addition, the TLI and OPD scores are correlated. The OPD is also related to OUD in both sexes. As expected, the CFI and OPD scores are correlated. In sum, the TLI score covaries with prodrome severity which, in turn, correlates with OUD diagnosis.

Multivariate Model

Table III shows that the 3 models have good fit; however, models 1 (no sex differences) and 3 (all parameters are free, ie, allowed to differ) are somewhat superior to model 2 (only path coefficients are equal). Models 1 and 3 do not differ in their fit (the difference χ^2 = 17.12, df = 17, P = .42). Whereas both models are statistically acceptable, we adopted model 1 because it allows including female participants in the analysis that would not be otherwise possible with model 3 because of the relatively small subset who developed OUD.

As indicated by the path coefficients (Figure), number of parents with substance use disorder predicts the TLI score (β = 0.26, P < .001), which, in turn, is correlated with OPD (r = 0.53, P < .001) and CFI (r = 0.32, P < .001) scores as well as predicts OUD nine years later (β = 0.39, P < .001). As expected, OPD and CFI scores, the 2 facets of the OUD prodrome, are correlated (r = 0.45, P < .001); however, only the CFI predicts OUD (β = 0.17, P < .001) when TLI score is taken into account. The results of this analysis are summarized in Table IV.

TLI mediates the association between number of parents with substance use disorder and OUD outcome in their children (β = 0.10, z = 4.62, P < .001). In effect, magnitude of familial loading for substance use disorder covaries with TLI score quantifying transmissible liability. In addition, CFI mediates the relationship between number of substance use disorder parents and their children's OUD diagnosis (β = 0.03, z = 2.83, P = .005). This finding demonstrates that the CFI is a valid measure of the OUD prodrome and related to magnitude of intergenerational risk.

Table II. Bivariate correlations among number of SUD parents and child's TLI, OPD, CFI, and OUD

	TLI	OPD	CFI	OUD
	r (*P* value)	r (*P* value)	r (*P* value)	r (*P* value)
Boys				
SUD parents	.32 (<.001)	.27 (<.001)	.25 (<.001)	.10 (.06)
TLI		.74 (<.001)	.46 (<.001)	.32 (<.001)
OPD			.53 (<.001)	.36 (<.001)
CFI				.34 (<.001)
Girls				
SUD parents	.24 (.004)	.36 (<.001)	.24 (.002)	.08 (.32)
TLI		.70 (<.001)	.24 (.008)	.20 (.03)
OPD			.40 (<.001)	.21 (.01)
CFI				.25 (.006)

Table III. Fit statistics of path models

Model	χ^2	Df	*P*	RMSEA	Comparative fit index	Tucker-Lewis index
1	17.58	19	.55	<.001	.99	.99
2	14.75	11	.19	.032	.99	.98
3	0.46	2	.79	<001	.99	.99

RMSEA, root mean square error of approximation.
Model 1 assumed that all path coefficients, means, and variances are equal between boys and girls. Model 2 assumed that only the path coefficients are equal. Model 3 assumed that all parameters are free.

To evaluate the utility of the predictors for forecasting OUD while taking into account their correlations, we applied the parameters obtained in path analysis to a logistic regression model. The respective ORs for the TLI and CFI are 1.47 (95% CI 1.30-1.66) and 1.83 (95% CI 1.07-1.31), respectively. As shown in Table V (available at www.jpeds.com), the receiver operating characteristic analysis based on the total sample demonstrates prediction sensitivity and specificity of 87% and 62% with overall accuracy of 86% (95% CI 73%, 99%) using a cut-off score of 5.5%. The 5-fold cross-validation results reveal a mean overall prediction accuracy of 89% (SD = .15) with bootstrap bias-corrected 95% CI (45%, 93%) using a cut-off score of 6%. Sensitivity and specificity are 75% and 89%, respectively. Notably, the AUC difference between the total sample and 5-fold mean is only 3%.

Post hoc analyses were additionally conducted to evaluate the accuracy of the predictor variables for detecting youths who developed alcohol and cannabis use disorder. These latter disorders were present in 25.1% and 22.5% of the sample at 25 years of age. The analyses were limited to these 2 outcomes owing to insufficient number of other drug disorders. With respect to alcohol use disorder, overall prediction accuracy was 68% (70% sensitivity and 55% specificity). Overall prediction accuracy for cannabis use disorder was 75% (76% sensitivity and 58% specificity). Thus, consistent with general liability to addiction, the variables forecasted 3 categories of substance use disorder, although most accurately for OUD.

Discussion

Cost-efficient prevention of OUD is contingent on identifying the high-risk segment in the general population. The polygenic risk score, aggregating information on genetic polymorphisms identified in genome-wide association

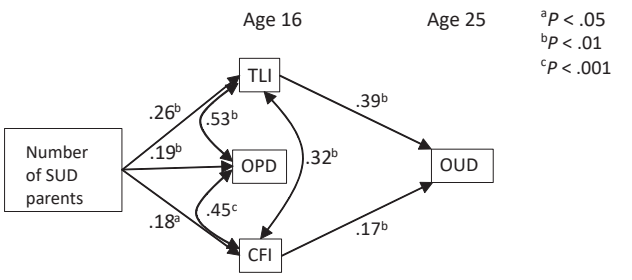

Figure. Path model depicting the relationship among parental SUD, child's TLI, CFI, and OPD score at 16 years of age on OUD diagnosis at 25 years of age.

Table IV. Logistic regression analysis for predicting opioid use disorder at age 25 years by TLI and CFI

	B	SE	OR	*P* values	95% CI
TLI	.39	.06	1.47	<.001	1.30, 1.66
CFI	.17	.05	1.18	<.001	1.07, 1.31

studies,[33,34] is one approach. However, because heritability of OUD liability is not high (less than 0.25)[29] owing to large functional distance between gene expression and the liability phenotype, it is not surprising that the polygenic risk score is insufficiently accurate for use in clinical practice. An alternative strategy adopted herein focuses on the liability phenotype. Within this measurement framework, the 5-fold mean results indicate that transmissible (intergenerational) risk and substance use in 16-year-old youths conjointly predict OUD at 25 years of age with 89% accuracy.

Results obtained in other studies also demonstrate that it is feasible to predict OUD.[35,36] The Opioid Risk Tool[37] shows very high accuracy; however, like most screening instruments, its use is circumscribed to patients taking opioids prescribed by a physician to manage pain. A more serious limitation is that symptoms of dependence, included in the set of predictor items, may not yet be present in high risk youths. The high sensitivity and specificity (>.80) reported for this risk assessment tool may, thus, partly be due to the fact that the person is close to or beyond diagnostic threshold for OUD, especially considering that only 2 symptoms are required in the DSM-5 taxonomy for diagnosis. The present study extends this line of research by showing high predictive accuracy a decade after evaluation of liability and prodrome using brief measures that can be self-administered using any device connected to the internet. Risk assessment can, thus, be expeditiously conducted prior to prescribing an opioid and subsequently at the time of each refill.

In addition, it is noteworthy that the TLI includes indicators of social deviancy. This is important considering that opioid users often violate the law by consuming medicinal opioids without physician prescription or using Schedule I formulations. Notably, severity of externalizing disorder in childhood covaries with magnitude of risk for developing opioid dependence in adulthood.[38] Hence, the TLI may also be useful for screening youths in the juvenile justice system to measure risk for OUD and other addictions. In sum, this study extends research findings into practical application by showing that the indicators of risk for substance use disorder can be assessed in childhood, and by adolescence, when substance use typically begins, the likelihood of advancing to diagnosis can be accurately determined.[39,40]

Recent survey data indicate that approximately 22.3 million Americans are in recovery from substance misuse, within which 5% report that opioids were the main problem.[41] The same survey found that 51%, 11%, and 10% of individuals in recovery reported that alcohol, cannabis, or cocaine was the main problem. The ancillary results obtained in this study further suggest that it is feasible to identify youths at high risk for these disorders, although predictive accuracy for alcohol and cannabis disorders may requires additional measurement refinement. Nevertheless, within pediatric practice, consisting largely of health maintenance and well check-up visits, identifying high risk youths[42] is consistent with the recommendation of the American Academy of Pediatrics.[43] In effect, in 15-20 minutes it is feasible to quantify risk for OUD and concomitantly current severity of substance use and associated health, psychological, and social adjustment problems.

Several caveats and limitations of this study are noted. Whereas the results lend confidence to the feasibility of routine risk screening, it should be noted that although sensitivity is high (87%), specificity is somewhat low for the total sample. A k-fold cross-validation provided somewhat different results: sensitivity was 75% and specificity was 89% with similar cutoff scores. In effect, false positive rate is 38% for the total sample, whereas it is 11% for the 5-fold cross-validation. In the light of differences, we observed in sensitivity and specificity between the total and cross-validation samples, the generalizability of the predictive model for new samples should be interpreted with care. In particular, caution must be exercised before denying intervention based solely on the results of this assessment. Even though a false-positive conclusion regarding OUD prediction is less costly than nondetection of a true-positive case, further research focusing on improving measurement precision is required, particularly directed at youth in the low-risk area of the liability distribution.[44] In addition, the sample is relatively small (n = 627), which may have inflated parameter estimates and decreased statistical power. Also, despite the importance of sex differences in substance use disorder etiology and natural history,[45-47] the size of the female sample (n = 135) did not allow for sex-specific multivariate analyses, although the equally good fit of the model with the absence of sex differences and the free-parameter model may be due to the lack of power. This limitation notwithstanding, the male and female participants are indeed very similar with respect to the predictor variables, IQ, socioeconomic status, and ethnicity. Nevertheless, research remains to be conducted to determine whether the accuracy of forecasting OUD using the TLI, CFI, and OPD is sex-specific. Furthermore, it should be noted that the participants were identified through proband fathers who either qualified for substance use disorder or had no disorder. The advantage of the high-risk paradigm is that it enables expeditiously accruing a sample of youths who develop substance use disorder. Nonrandom recruitment may, however, have produced results that are not generalizable to the population. Even though this possibility cannot be fully discounted, it is noteworthy that many studies conducted on this cohort conform to results obtained by other investigators. Lastly, OUD liability was measured by the TLI after substance use onset. Although this may have influenced the propensity to endorse certain characteristics, deferring risk assessment until midadolescence was necessary to include prodrome severity in the prediction model.

In summary, the index of transmissible liability to substance use disorder combined with past 30-day frequency of overall substance use detects 16-year-old youths who qualify for OUD at 25 years of age with 86% accuracy. Considering that this assessment can be self-administered

on the web platform, currently under development, this protocol may be useful for large scale or routine screening to detect high-risk youths requiring prevention intervention. ■

Submitted for publication Aug 20, 2019; last revision received May 1, 2020; accepted Jul 7, 2020.

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Infantile Diarrhea

Lifshitz F, Coello-Ramírez P, Gutiérrez-Topete G. Monosaccharide intolerance and hypoglycemia in infants with diarrhea I. Clinical course of 23 infants. J Pediatr 1970;77:595-603.
Lifshitz F, Coello-Ramírez P, Gutiérrez-Topete G. Monosaccharide intolerance and hypoglycemia in infants with diarrhea. II. Metabolic studies in 23 infants. J Pediatr 1970;77:604-2.

In 1970, Lifshitz et al described the clinical course of 23 infants with gastroenteritis, carbohydrate intolerance, and diarrhea. In these infants, diarrhea resolved after removal of dietary carbohydrates. Notably, 17 infants experienced hypoglycemia, which improved with diarrhea resolution. Dietary glucose re-introduction was tolerated in all but 9 infants who died before proving full tolerance. The study concluded that patients with diarrhea had monosaccharide and disaccharide intolerance that improved with total dietary carbohydrate elimination. Thus, impairment of carbohydrate absorption by the small intestine causes the carbohydrate load to pass into the colon. There, bacterial fermentation promotes the production of lactic acid, which decreases the intraluminal pH, causing an osmotic diarrhea. However, further metabolic studies concerning the nature of hypoglycemia were needed. This was described in the second article; the authors determined that factors affecting blood glucose include carbohydrate intolerance, glucose amount introduced, and dietary intake, as well as glycogen stores in the liver.

The question of what to feed a child with acute diarrhea still arises in everyday practice. We now have more information on the causes of nutrient malabsorption during acute diarrheal illness. In 1983, Lo and Walker described chronic protracted diarrhea of infancy as an iatrogenic, nutritional disease.[1] They described diarrheal diseases that improved with bowel rest—in effect, removal of high osmolality contents from the intestinal lumen. However, bowel rest must be accompanied by appropriate nutrition provision, either intravenously only, or intravenously plus small amounts of continuous intraluminal feeds, which allows mucosal healing. In 1984, Fagundes-Neto et al provided insight on the histology of the small intestine during protracted diarrhea.[2] They reported alterations of the intestinal mucosa, disaccharidase deficiency, and disruption of the intestinal permeability barrier; they proposed that severe deterioration of nutritional status and death is possible if appropriate treatment is not established. In 2018, a Clinical Guideline from the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition reviewed recommendations on the management of acute diarrhea in nonmalnourished children and determined that elimination diets are usually not indicated for children with acute gastroenteritis because this may further impair the child's nutritional status.[3]

In summary, the key best practice point over the past 50 years is that appropriate early nutrition during diarrheal illness is essential for recovery. If oral or enteral nutrition is limited owing to the disease process, appropriate temporary parenteral provision of nutrients is necessary to allow for appropriate healing and recovery.

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Table V. Results of receiver operating characteristic analyses based on total sample and 5-fold cross validation

	AUC	Sensitivity	Specificity	Cut-off score
Total sample	86%	87%	62%	5.5%
Average across 5 folds	89%	75%	89%	6%