IMPULSIVE AGGRESSION AND THE INCIDENCE OF EARLY-ONSET DEPRESSION IN YOUTH

by

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Objective: To assess the relationship between impulsive aggression (IA) and the early-onset depression (OD) in youth.

Method: The data consists of records from 348 youth aged 10 to 25 years who had never had a mood disorder by the time of study entry, but had at least one parent with a diagnosed mood disorder. The participants were recruited at two different sites. The primary outcome was OD and the primary measure of interest was IA. The effect of the baseline IA level was evaluated univariately and after adjusting for other risk factors associated with OD. Univariate analyses of the effect of categorical factors were performed using log-rank and Wilcoxon tests, with the corresponding tests for trends being implemented for ordinal variables. Multivariable modeling was done using the discrete-time proportional hazards model. Optimal dichotomization of IA into high and low risk groups was obtained using the outcome-oriented technique by Contal and O'Quigley.

Results: Univariate analyses indicated that participants with a high level of impulsive aggression had an increased risk of OD (hazard ratio (HR) = 2.0, 95% CI: 1.13 to 3.55). Increased risk for youth with high IA was observed after adjusting for site, offspring risk factors of behavior disorder and puberty, proband risk factors of anxiety disorder and alcohol/substance abuse. Among these factors, only one, behavior disorder, alleviated the effect of IA. Behavior disorder was strongly associated with high risk for depression (HR = 2.51, 95% CI: 1.32 to 4.77) and

behavior disorder and IA were closely related, with the rate of behavior disorder in the high IA group being significantly greater than in the low IA group (26.5% vs. 9.4%, $p < 0.001$).

Conclusions: The results suggest that impulsive aggression is a significant prognostic factor for depression onset. Although part of the information carried by the IA measurement is captured by other measurements (e.g., behavior disorder), the level of IA still offers useful information regarding the future depression onset.

Implication for public health: An understanding of the relationship between impulsive aggression and depression onset is important for the treatment and prevention of depression.

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1.0 INTRODUCTION

Major depression is one of the most common mood disorders and currently no fully satisfactory treatments for major depression are available (Kupfer et al., 2012). Unipolar depression is the second leading cause of disability worldwide and the leading cause of disability in the United States (Gonzales et al., 2010). Depression is closely related to suicide attempts and adolescence depression symptoms convey an increased risk of suicidal behavior (Thapar et al., 2012). Untreated depression, therefore, could be an important contributor to the risk of suicide in adolescents.

In addition to early-onset mood disorder, a tendency of impulsive aggression has also been recognized as a important contributor to the risk for suicidal behavior, especially in adolescents and young adults (Brent et al. 2002; Mann et al., 2005; McGirr et al., 2007 & 2008; Melhem et al., 2007; Turecki et al., 2005). In the stress-diathesis model of suicidal behavior, depression and IA are thought of as two relatively independent risk factors that, when they co-occur, markedly elevate the risk for suicidal behavior (Mann et al., 1999). However, more recent findings have suggested that depression and impulsive aggression (IA) are not completely independent, either because they share certain etiological factors, or because the presence of one (e.g., depression) affects the other. Some studies have found that aggression, impulsivity, and behavioral disorders are precursors to juvenile onset depression (Chronis-Tuscano et al., 2010; Harrington et al., 1997; Jaffee et al., 2002). In a cross-sectional analysis for the study used in this

project, it was found that IA level was associated with an early onset of mood disorder including depression and bipolar disorder (Brent et al., 2004). However, in general there are a paucity of studies that examine the relationship between IA and onset of depression (OD).

This project was part of "Familial Pathways to Early-Onset Suicide Attempts" (FAMPATH) study, which seeks to identify familial and individual precursors of early-onset suicidal behavior and mechanisms by which suicidal risk is transmitted from parent to child. The assessment of depression and IA were performed simultaneously in this study. We applied survival analysis techniques to examine the effect of IA on depression onset in offspring without a previous history of depression and bipolar disorder. In particular, we sought to examine whether IA contributes to an increased risk of OD, both univariately and in the context of other baseline characteristics that may influence this relationship.

2.0 ORIGINAL STUDY DESCRIPTION

This project was based on a subset of the FAMPATH data (up to year 2008) composed of 348 offspring aged from 10 to 25 years (mean = 14.3 years; standard deviation [SD] = 4.0 years) from 225 probands with mood disorders, around half of whom also had a history of suicide attempt. The majority of the participants were recruited from inpatient units at Western Psychiatric Institute and Clinic in Pittsburgh, and at New York State Psychiatric Institute in New York City. The remaining subjects were recruited from advertisements and from outpatient clinics or partial hospitalization programs in Pittsburgh and New York. We excluded offspring with a prior history of unipolar or bipolar disorder or a suicide attempt, in order to avoid the possible influence of these diagnoses in the assessment of the effect of IA on OD. Institutional Review Board approval was obtained from all involved institutions, and written informed consent/assent was obtained from all participants.

In this study, a direct interview was conducted with probands and offspring participating in the study at baseline and at yearly follow-ups. All interviewers were at least master's degree level clinicians or psychiatric nurses who received extensive training in interview administration. Participants also completed several self-reported questionnaires at around the same time of the interview. All offspring were followed-up a mean of 2.7 years (SD = 2.0, range = 1 - 8) or 932 total person-years.

2.1 PRIMARY OUTCOME

The primary outcome was depression onset, which was defined as the first recorded time point when offspring were diagnosed with either major depressive disorder (MDD), or dysthymic disorder, or depression disorder not otherwise specified. Depression was assessed during the interview using the Structured Clinical Interview for DSM-IV (SCID-I) for participants age 18 and older (First et al., 1996), and using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) for those under 18 (Kaufman et al., 1997).

2.2 PRIMARY VARIABLE AND OTHER COVARIATES

Our primary measure of interest was impulsive aggression (IA) which was defined as "the tendency to respond with hostility or aggression to frustration or provocation", and was measured by the Buss Durkee Hostility Inventory (BDHI) self-report with a total score ranging from 0 to 75, with higher scores indicating more severe status (Buss and Durkee, 1957). In youth under age 14, a downward extension of this measure, the Children's Hostility Inventory (CHI) with a total score ranging from 0 to 38 was used (Kazdin et al., 1987). Two other measures related to IA, namely impulsivity and aggression were also collected. Impulsivity was assessed with the Barratt Impulsivity Scale (BIS) in participants 18 and older (Barratt, 1965), and with the impulsivity subscale of the Inattention/Overactivity With Aggression Conners Teacher Rating Scale (IOWA) or Emotionality Activity, Sociability and Impulsivity inventory (EASI) in those

aged 10 to 17 (Pelham et al., 1989). Aggression was measured using the Brown-Goodwin Lifetime History of Aggression (BGLHA) in all participants (Brown and Goodwin, 1986).

Table 1 lists the other domains and their corresponding assessment instruments relevant to this project. Self-reported depressive symptoms were assessed using the Beck Depression Inventory (BDI) and, for those younger than 14, the Children's Depression Inventory (CDI) (Beck et al., 1988; Kovacs et al., 1985). Depressive symptoms were also assessed by interview using the Hamilton Depression Inventory (HAM) (24 items) and, for those younger than 18, the Children's Depression Rating Scale-Revised (CDRS-R) (Hamilton, 1960; Poznanski et al., 1985). Hopelessness was assessed using the Beck Hopelessness Scale (BHI) and, for those younger than 14, the Children's Hopelessness Scale (CHPLS) (Beck et al., 1974; Kazdin et al., 1986). Intercurrent negative life events were assessed with the shortened version of the Social Readjustment Rating Scale (SRRS) in participants 18 and older, and the Life Events Checklist (LECL) for those under age 18 (Lewinsohn et al., 1991). History of suicidal behavior was assessed with the Columbia University Suicide History Form, the Medical Damage Lethality Rating Scale, and the Beck Suicide Intent Scale in probands and offspring 10 and older (Beck et al., 1974; Mann et al., 1992). History of physical or sexual abuse was assessed in all participants from the posttraumatic stress disorder section of the psychiatric interview and the Abuse Dimensions Inventory (Chaffin et al., 1997).

Puberty was assessed using the Petersen Pubertal Development Scale (Petersen et al., 1988) and score items were summed and averaged with a range from 1 to 4, with higher scores associated with greater maturity. Other axis I disorders besides depression diagnosis were diagnosed using the SCID-I and K-SADS-PL diagnostic interviews. Behavior disorder was

defined as the presence of any of the following: conduct disorder, oppositional defiant disorder (ODD), and attention deficit hyperactivity disorder (ADHD).

Table 1. Study instruments

Domain assessed	Instrument	Participant
Current and Lifetime Axis I Disorders (DSM-IV) ††	Structured Clinical Interview for DSM-IVs	Offspring ages ≥18
	Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version	Offspring ages 10-17
Impulsive Aggression†	Buss-Durkee Hostility Inventory	Offspring ages ≥14
	Children's Hostility Inventory	Offspring ages 10-13
Impulsivity†	Barratt Impulsivity Scale	Offspring ages ≥18
	Iowa-Conners Parent Physical Report, Impulsivity Subscale	Offspring ages 10-17
	Emotionality, Activity, Sociability, and Impulsivity scales	Offspring ages 10-17
Aggression††	Brown-Goodwin Lifetime History of Aggression and its Follow-up form	All participants
History of Suicidal Behavior††	Columbia University Suicide History Form and Medical Damage Lethality Scale	All participants
Self-reported Depressive Symptoms†	Beck Depression Inventory	Offspring ages ≥14
	Children's Depression Inventory	Offspring ages 10-13
Hopelessness†	Beck Hopelessness Scale	Offspring ages ≥14
	Children's Hopelessness Scale	Offspring ages 10-13
Anxiety††	Scale for Childhood Anxiety-Related Disorders	Offspring ages ≤18
Interview-rated Depressive Symptoms††	Hamilton Depression Inventory (adult version)	Offspring ≥18
	Hamilton Depression Inventory (child version)	Offspring ages 10-17
	Children's Depression Rating Scale-Revised	Offspring ages 10-17
History of Physical and Sexual Abuse††	Childhood Experiences Questionnaire	Offspring ages ≥18
	Abuse Dimensions Inventory	Offspring ages ≥18
	demographic questionnaire	Offspring ages ≥18
	Psychosocial Schedule	Offspring ages 10-17
Family Functioning†	Family Adaptability and Cohesion and Evaluation Scale-II	Offspring
Lifetime History of Non - Suicidal Self-Injury†	Self-Injurious Behavior Scale	All participants

††Interview-rated; † Self-reported

2.3 Z TRANSFORMATION FOR CONTINUOUS VARIABLES

Different instruments were used to measure variables for different age groups. In order to provide a consistent quantification of continuous parameters (e.g. IA), measurements from the instruments that examined the same content area but at different ages were standardized. For each measuring instrument, its standardized *z*-score was computed by subtracting the mean of all available observations (including longitudinal ones) for the 348 offspring in this study, then dividing by the corresponding standard deviation ($z = [x - \mu] / \delta$). Standardized *z*-scores for IA, impulsivity, self-reported and interview-rated depressive symptoms, hopelessness, and intercurrent negative life events were calculated. Table 2 lists the scale of the different instruments for which *z*-scores were computed; higher scores indicating more severe status.

Table 2. The scales of the instruments for variables to be standardized

Variables	Instrument*
Impulsive Aggression	BDHI (0~75) / CHI(0~38)
Impulsivity	BIS (0~120) / IOWA (0~45) / EASI (0~100)
Interview-rated Depressive Symptoms	HAM (0~75) / CDRS-R (0~113)
Self-reported Depressive Symptoms	BDI (0~63) / CDI (0~54)
Hopelessness	BHI (0~20) / CHPLS (0~17)
Life Events	LECL (0~31) / SRRS (0~12)

*Numbers in parenthesis indicate the range of possible scores for each measure

3.0 METHODS

3.1 ANALYTICAL STRATEGY

The first onset of depression (OD) was defined as the failure event, and time to event was measured from entry into the study to the date of the interview when depression onset was reported. For offspring without depression onset, the time was censored on the date of the last recorded interview. The overall analytical strategy followed the following major steps:

1. Generation of basic descriptive statistics for the data
2. Univariate analyses of the baseline level of IA as a predictor of time to OD
3. Construction of the multivariable models for time to OD
4. Investigation of the adjusted effect of baseline IA on time to OD
5. Sensitivity and secondary analyses.

Several features of the collected data had driven specific approaches within the steps listed above. First, our primary analysis was based on the discrete time to event methodology, while the conventional continuous time to event analysis was used to verify the consistency of the findings. According to the design of the original study, participants attended annual appointments; hence time to OD can be measured either in days or years. As a result, time to OD can be analyzed using either continuous- or discrete-time to event approaches. In this setting the

discrete time to event analysis was preferable for both interpretational and technical reasons (Allison, 1982). Second, we standardized the IA measurements to the same scale using the *z*-transformation (Section 2.3), because the IA was measured on different continuous scales for different offspring age groups (Table 1), and because the small sample size (47 observed events) prohibited meaningful analysis by individual age-groups. Furthermore, we mainly considered discretized versions of the continuous variables because the small sample size prevented reliable identification of appropriate functional form of their continuous effects. Finally, for primary analyses we imputed the missing values from two related covariates, aggression and impulsivity, using linear regression, since IA measurements had a number of missing observations. The robustness of the final results with respect to the imputed values was verified in the sensitivity analysis in step (5).

Below we outlined the specific methods used for each of the analytical steps listed above. The corresponding statistical analyses are conducted using SAS v.9.2.

3.1.1 Descriptive statistics

The goal of this step was to describe the data and identify any patterns that could affect the analysis. We summarized the incidence rate of OD overall and by three age-groups, the number of offspring at risk of depression, and the number of participants who developed depression or were censored. We examined the distribution of standardized IA after *z*-transformation overall, and in each age-group. We used t-Test and Fisher's exact test or Pearson's Chi-square test, where appropriate, to compare the characteristics of offspring who had been lost to follow-up and offspring who had stayed in the study at least 1 year.

3.1.2 Univariate analysis of baseline IA levels and OD

The primary objective of this step was to determine whether the baseline level of IA was associated with time to the first OD. For most robust inferences we analyzed categorized levels of standardized IA (in two, or more categories) with non-parametric log-rank and Wilcoxon test and corresponding tests for trend. We used discrete time (years) for the primary analysis and verified the consistency of the findings for continuous time (days since the study entry).

The considered categorizations were obtained by using percentiles and an optimal dichotomization approach by Contal and O'Quigley (1999). Data-oriented dichotomization methods such as median-split tend not to perform well in general, and we did not have clinical indications for selecting a specific IA cutpoint in this study. Therefore, we used the outcome-oriented method by Contal and O'Quigley for estimating the dichotomization that maximizes separation between high and low risk IA groups. In this project, this method was implemented using the published SAS macro (Mandrekar et al., 2003).

Life-table estimates and log-rank test (proc lifetest) were used to compare the OD-free survival between high and low IA risk groups in all offspring, and in three age groups (10 to 13, 14 to 17, and 18 to 25 years old). Both continuous IA and dichotomized IA groups were assessed in the discrete survival analysis (proc logistic) and standard Cox proportional hazards model (proc phreg). To investigate the possible presence of dose-response relationship we analyzed ordinal representation of IA in the framework of the proportional hazards model for discrete and continuous time to event.

3.1.3 Multivariable models

The primary objective of this step was to build multivariate models for the evaluation of the adjusted effect of the IA on time to OD. For this purpose, the variable of primary interest (IA) was excluded from the model building steps and its effect was assessed when added to the already built model. In order to better understand the nature of the effect of IA and its association with other parameters we considered the following types of models: 1) with only demographic or historical offspring predictors, 2) with any measured offspring parameters, including DSM-IV diagnosis and clinical measurements, and 3) with both offspring- and proband-level measurements.

Proportional hazards model was used to assess the effects of IA and other variables on time to OD. Baseline variables which were univariately significant at $\alpha = 0.1$ were included in the multivariable model selection, and $\alpha = 0.05$ was used to select variables in the final model. A backward selection approach was applied for the multivariable survival model building. Multivariable models selection followed the standard procedure (Hosmer et al., 2008), considering confounders and interactions between variables.

3.1.4 Investigation of the adjusted effect of the baseline IA

The objective of this step was to use the multivariable models to investigate whether the effect of IA changed quantitatively and/or statistically after adjustment for sets of other risk factors. The IA variable was added last to all multivariable models to assess its prediction impact to OD.

We adjusted for intracluster correlation of proband using generalized estimating equation (GEE) in our multivariable survival models because often more than one offspring per proband

participated in the study. Observations for the offspring of each proband were considered as a exchangeable correlation structure.

3.1.5 Sensitivity and secondary analyses

The objective of this step was to evaluate the sensitivity of the results to the assumptions used in previous analytical steps, to examine clinically important associations, and to improve the interpretation of the findings. First, we verified the consistency of our findings with the results from the continuous-time (instead of discrete-time) survival analysis. Next, we evaluated the sensitivity of our results with respect to the elimination of the observations with imputed values. Next, we assessed the adjusted effect of the ordinal IA variable and evaluated the sensitivity of the model estimates with respect to change of the functional form of continuous covariate(s). Finally, we examined the relationship of IA on OD based on the subset of data corresponding to a single offspring per family. In the secondary analyses, we assessed the dose-response relationship between IA and OD, evaluated the relationship between IA and behavior disorder; and explored the role of sex in the effect of IA on OD.

3.2 METHODS USED IN ANALYSIS

3.2.1 Cox proportional hazards model

Cox proportional hazards model is a standard method to analyze time to event data (Cox, 1972). The Cox model accounts for baseline and prognostic covariates incorporated into the model. The

hazard function, which is the instantaneous rate of event for people at risk at time t, is defined as $\lambda(t)$. The hazard for subject *i* at time *t* is:

$$\lambda\left(t \middle| X = x_i\right) = \lambda_0\left(\mathrm{t}\right)\exp\left(\mathrm{X}\beta\right)$$

Where $\lambda_0(t)$ is the unspecified underlying baseline hazard (or hazard when all covariates have the value zero), $x_i = (x_1, x_2, \ldots, x_p)$ is a vector of p covariates for the i^{th} person, and $\beta = (\beta_1, \beta_2, \ldots, \beta_p)$ is the corresponding set of regression coefficients estimated from the data. Hazard ratios (HR) greater than one indicate that a variable is associated with an increased rate of the event, and hazard ratios less than one indicate a decreased rate of the event.

The Cox model assumes proportional hazards, that is the ratio of the hazards for two subjects *i* and *j* is constant over time. Statistical tests and graphical methods such as plotting the log cumulative hazard function (log[-logS(t)]) can be used to assess the proportional hazards assumption; here, S(t) is the survival probability that an individual survives at least to time t.

3.2.2 Discrete survival analysis

Sometimes survival time is not observed precisely, especially in studies when follow-up visits occur at the end of fixed intervals (hence, the events are known to happen within the intervals). This kind of data form is often known as interval-censored or grouped data. Each subject's survival time is treated as a distinct observation. For this kind of data, a discrete analog of continuous proportional hazards model based on a binary response model with complementary log-log (c-log-log) link function is suggested by Prentice and Gloeckler (1978) as

$$\log[-\log(1-P_{it})] = \alpha_t + \beta x_i$$

Here, the P_{it} is the conditional probability that the i^{th} subject has an event in the t^{th} time interval, given that he/she did not have an event before. t =1, 2, 3 … is the discrete unit of time. α_t is a constant related to P_{it} in the interval t for the i^{th} subject when x_i =0. β is the log of the hazard ratio within the time interval as defined in the Cox proportional hazards model.

3.2.3 Best dichotomization of a continuous predictor in time-to-event setting

In medical and epidemiological research, it is often beneficial to categorize a continuous variable such as age and BMI. Continuous variables are often dichotomized by selecting a cutpoint to group people into high risk and low risk groups. The discretization of continuous variables helps interpret the results and improve the robustness of statistical inferences. One major question is how to determine the cutpoints. Biological reasoning is the best strategy to choose cutoffs, but the necessary indications are rarely available. When there are no biological reasons, data-oriented and outcome-oriented methods are two strategies to dichotomize a continuous variable. Data-oriented methods are based on certain quartiles such as the median and upper quartile; however, these splits tend not to perform well. Outcome-oriented methods are based on test statistics such as log-rank, score, likelihood ratio and Wald statistics. These test statistics can be used to find the cutpoint to achieve the most significant relationship between variables of interest and outcome.

Contal and O'Quigley proposed to determine the optimal threshold by maximizing the log-rank test statistic corresponding to all possible dichotomizations of a continuous variable, and to evaluate the statistical significance of the effect of the dichotomized variables by p-value for the maximum of the log-rank statistic (i.e., adjusted for the multiple-comparisons bias). Suppose there are K distinct values of a continuous variable (X): each potential cutpoint C_k will

be used to divide the study population into two groups: subjects with X being less than or equal to the cutpoint, and subjects with X greater than the cutpoint. Let T be the time to event, and D the total number of distinct event times. At each event time, t_i, we calculate the total number of events, d_i, the total number at risk, r_i, the total number of events with X > C_k, d_i^+, and the total number at risk just prior to t_i with X > C_k, r_i^+. Thus, the log-rank statistic for some fixed C is given by:

$$L_k = \sum_{i=1}^{D} (d_i^+ - d_i \frac{r_i^+}{r_i})$$

The optimal cutpoint is that value of C_k that maximizes the absolute value of the log rank statistic L_k. In other words, C_k will be the value of the continuous variable that gives the maximum difference between the subjects in the two groups divided by this cutpoint. In order to evaluate the significance of the obtained cutpoint, Contal and O'Quigley suggest the following test statistic,

$$Q = \frac{\max |L_k|}{s\sqrt{D-1}}$$

Here, $s^2 = \frac{1}{D-1} \sum_{j=1}^{D} a_j^{\ 2}$ and the associated score $a_j = 1 - \sum_{i=1}^{j} \frac{1}{D-j+1}$.

This test statistic is adjusted for the bias of test outcome by choosing the optimal cutpoint C_k that maximizes the separation between the two groups. For Q > 1, the p-value is approximately equal to $2\exp(-2Q^2)$.

4.0 RESULTS

4.1 DESCRIPTIVE ANALYSIS

The overall FAMPATH study consisted of 660 offspring, but we excluded those over the age of 25 (N = 109), those younger than 10 (N = 15), and those who had previous or ongoing depression at the time of the baseline assessment (N = 201). We also excluded offspring with a lifetime diagnosis of bipolar disorder (N = 36), and suicide attempt at baseline (N = 47). Because individuals could be in more than one category, this resulted in 312 participants who were excluded and a total of 348 offspring who were included in this analysis. Among them, 44.5% were female; 66.7% were white; 10.3% were Hispanic. Forty-seven (13.5%) were observed to develop depression.

Forty-two youth were only assessed at baseline, and thus did not contribute to the analysis. Those offspring compared to the rest of the studied cohort were more likely to be Hispanic (14/42 (33.3%) vs. 22/304 (7.2%), Fisher's exact (FET), $p < 0.001$), female (25/42 (59.5%) vs. 130/306 (42.5%), $\chi^2_1 = 4.34$, $p = 0.047$), had lower puberty score (2.5 (SD = 1.0) vs. 2.9 (SD = 1.0), $t(326) = 2.37$, $p = 0.02$) and lower self-reported depression score at baseline (-0.2 (SD = 0.7) vs. 0.2 (SD = 1.1), $t(58.5) = 2.90$, $p = 0.01$).

The five-year depression-free survival rate was 76.6%. The age specific incidence rates of OD per 1000 person-years for offspring with age of 10-13, 14-17, and 18-25 years were 42,

62, and 56, respectively (Table 3). The estimated survival curves indicated that these three age groups had similar depression-free survival patterns (log-rank test, p = 0.40) (Figure 1).

Table 3. Age specific incidence rate of the OD

Age at baseline (years)	Number of offspring	Number of depression onset	Person years	Incidence rate per 1000 person years
10-13	180	19	457	42
14-17	86	15	243	62
18-25	82	13	232	56
Total	348	47	932	50

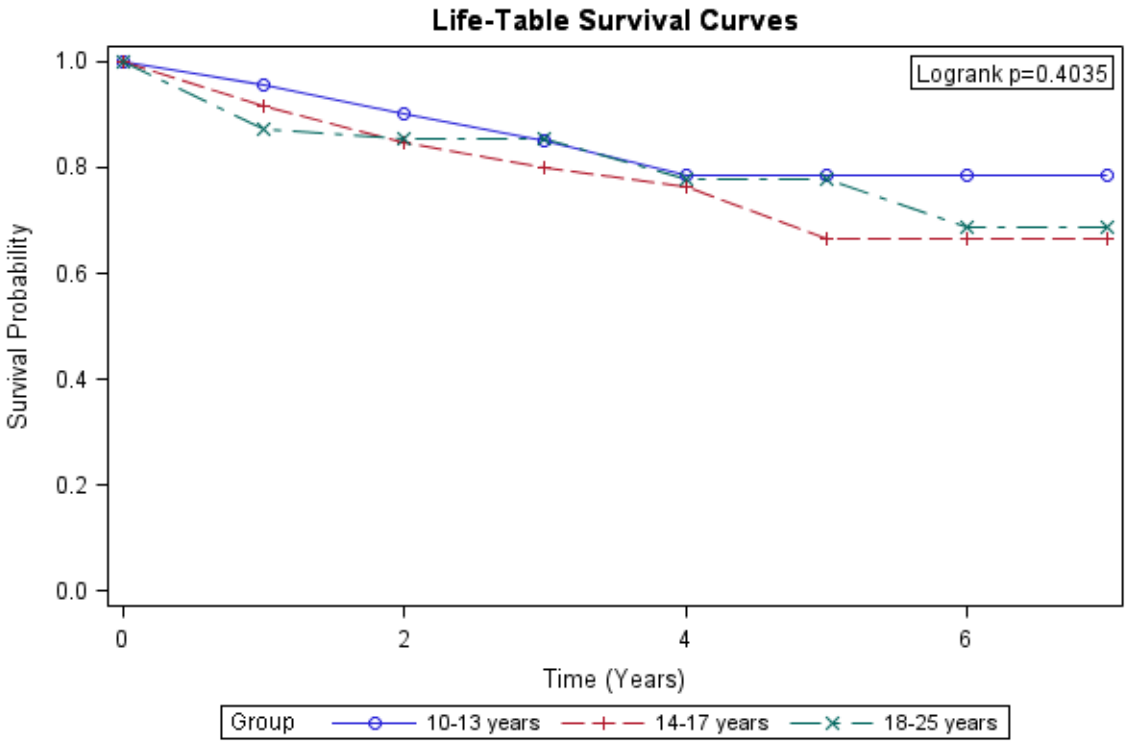


Figure 1. OD-free survival curves for the three age groups

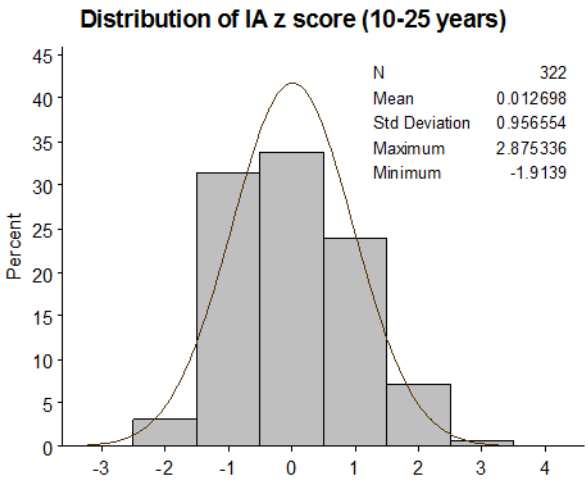
Out of the 47 offspring with observed OD, 32 developed depression at follow-up year 1 or year 2, and 15 developed depression after year 2 (Table 4). No offspring was observed to have OD after year 6. Censoring was due either to late entry in the study or lost to follow-up. The most common reasons for offspring to be lost to follow-up were death, incarceration, refusal to continue the study, unable to be contacted.

Table 4. Descriptive survival table for the OD

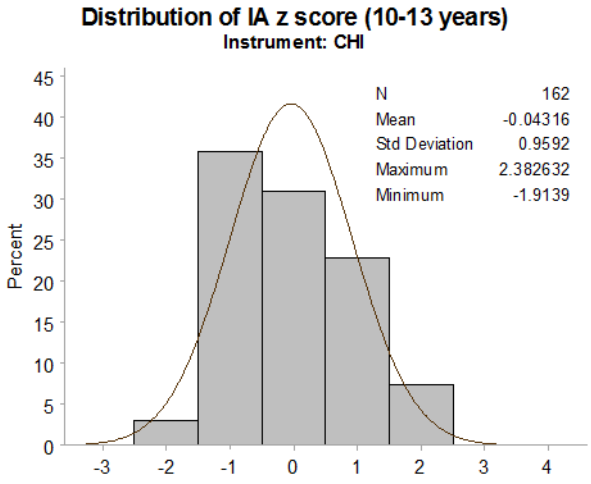
Years of follow-up	Number of offspring at risk	Number of offspring with depression onset	Number of offspring censored
Baseline	348	0	42
Year 1	306	21	48
Year 2	237	11	62
Year 3	164	6	55
Year 4	103	6	36
Year 5	61	2	26
Year 6	33	1	10
Year 7	22	0	16
Year 8	6	0	6

The mean [SD] of the standardized IA *z*-scores at baseline for all offspring was 0.01[0.96] (Figure 2a) and the median was -0.07. The mean [SD] of the IA *z*-scores at baseline was -0.04 [0.96], 0.10 [0.89], and 0.04 [1.02], respectively, for offspring with ages of 10 - 13, 14 - 17, and 18 - 25 years (Figures 2b, 2c, 2d). The sample means and variances of the IA *z*-scores for different age groups differed respectively from 0 and 1 due to the use of all longitudinal observations to generate the *z*-scores. The distribution of the IA *z*-scores for individual age-groups did not deviate substantially from the standard normal distribution. For 26 offspring with missing baseline IA scores, IA *z*-scores were imputed using linear regression based on reported levels of aggression and impulsivity.

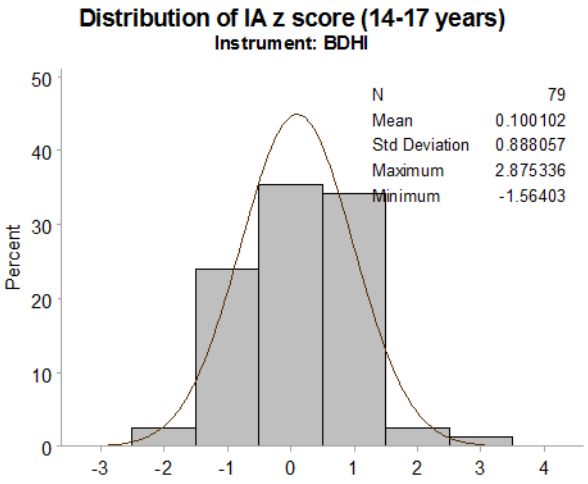
(a) All offspring



(b) 10 - 13 years



(c) 14 - 17 years



(d) 18 - 25 years

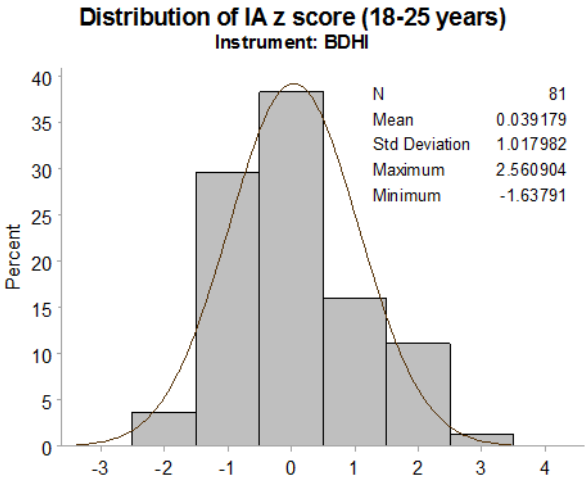


Figure 2. Histograms of IA scores in each age group at baseline

4.2 UNIVARIATE ANALYSIS OF IA

For the sake of robustness, initial analysis of the effect of the IA was based on dichotomized levels of baseline IA. The median-split and mean-split IA *z*-scores provided indication of

separation between high and low groups regarding depression-free survival time, especially at the early years (Wilcoxon test, p = 0.04 and 0.02, respectively; log-rank test p = 0.14 and 0.07, respectively).

Next we estimated the optimal dichotomization of IA *z*-scores to separate high and low risk IA groups using the Contal and O'Quigley method. A total of 120 distinct IA *z*-scores could be used as a potential cutpoint. Using the discrete time, 8 distinct timepoints (years) were observed and the maximum value of the log-rank statistic was also obtained at the IA *z*-score of 0.338 with a test statistic of 4.5 ($p < 0.001$) (Table 5). These results suggested that the IA cutoff was highly significant in the discrete time setting, and IA was associated with time to OD. For the continuous time, there were 269 distinct timepoints, and the maximum value of the log-rank statistic was attained at IA *z*-score of 0.338 with test statistics of 1.24 (p = 0.09). The corresponding IA *z*-score was 19 for offspring aged from 10 to 13 (CHI instrument), and 33 for those 14 and older (BDHI instrument). These two cutoffs are relatively close to the midpoint of the two original IA instrument scores (Table 6). The loss of the significance of the effect of the optimally dichotomized IA for continuous time may be due to non-proportional hazards of the continuous time.

Table 7 reports the descriptive survival table for the high and low IA groups. At follow-up year 1, 14 (out of 110) and 7 (out of 196) offspring developed depression in the high and low IA groups, respectively. At follow-up year 2, 5 (out of 84) and 6 (out of 153) offspring developed depression in the high and low IA groups, respectively. No OD was observed after follow-up year 5 for the high IA group, and follow-up year 6 for the low IA group.

Table 5. Results of the Contal and O'Quigley procedure

	Continuous time	Discrete time
IA z cutoff	0.338	0.338
p value (Contal and O'Quigley method)	0.09	<0.001*
p value (unadjusted log-rank test)	0.03	0.02*

*The result that p value from Contal and O'Quigley method was much smaller than that from log-rank test is counterintuitive. The publicly available SAS-macro (Mandrekar et al., 2003) was verified.

Table 6. The optimal IA cutoffs in the original instruments' scales

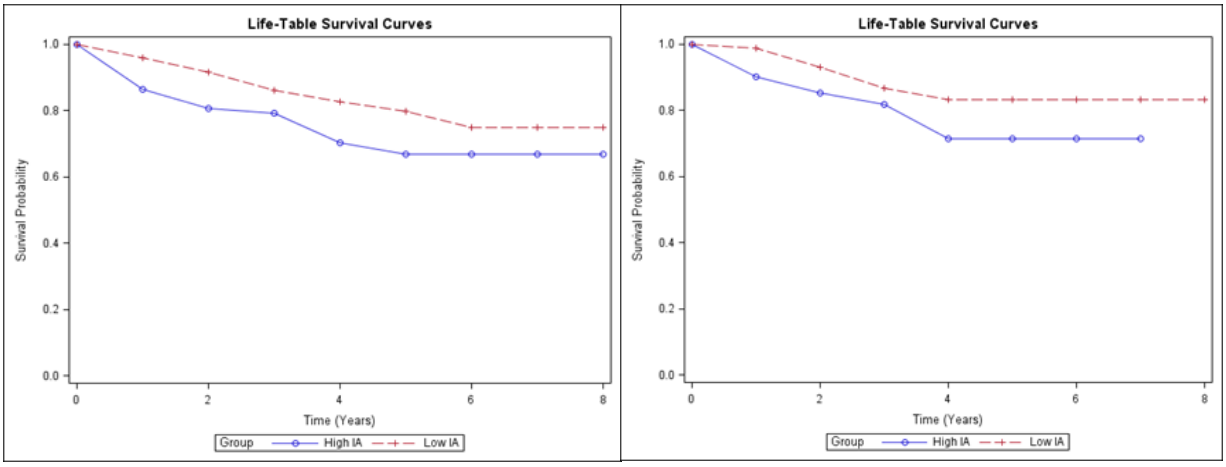
Age at baseline (years)	Instrument scales	Normal distribution where IA *z*-score were calculated Mean (SD)	Cutoff score 0.338 in original instrument scale
10-13	CHI (0-38)	16.47 (6.49)	19
14-17	BDHI (0-75)	29.35 (11.62)	33
18-25	BDHI (0-75)	28.67 (12.86)	33

Table 7. OD-free survival table for the low and high IA levels

Years of follow-up	Total number of offspring at risk	Low IA group		High IA group	
		Number of offspring at risk	Number of offspring with OD	Number of offspring at risk	Number of offspring with OD
Baseline	348	222	0	126	0
Year 1	306	196	7	110	14
Year 2	237	153	6	84	5
Year 3	164	103	5	61	1
Year 4	103	62	2	41	4
Year 5	61	35	1	26	1
Year 6	33	20	1	13	0
Year 7	22	12	0	10	0
Year 8	6	4	0	2	0

The estimated survival functions by the two IA groups indicated a clear difference in the overall survival functions (Figure 3a). The survival curves showed similar separation of high and the low IA groups at age 10 - 13, 14 - 17 and 18 - 25 years old groups (Figures 3b, 3c, 3d) with the early differences being more pronounced (log-rank test, p = 0.12, 0.13 and 0.34, respectively; Wilcoxon test, p = 0.01, 0.07, and 0.23, respectively). Using the discrete-time proportional hazards model by Prentice and Gloeckler (1978) we estimated the hazard ratio of the dichotomized IA to be 2.00 (95% CI: 1.13 to 3.55, p = 0.02).

(a) 348 offspring (b) 10-13 years



(c) 14-17 years (d) 18-25 years

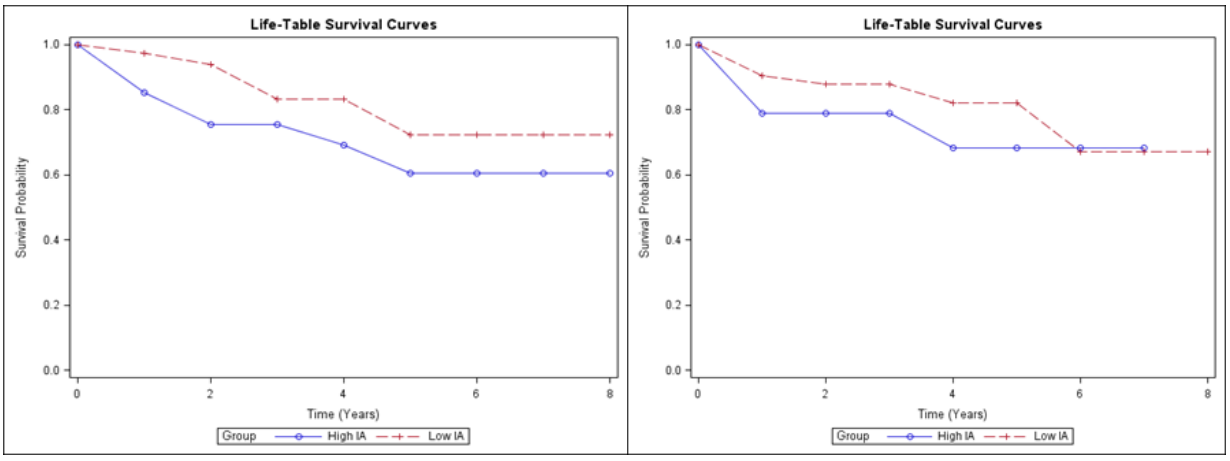


Figure 3. OD-free survival curves for high and low IA levels

We further investigated the dose-response effect of IA by discretizing the IA *z*-scores into 3 and 4 groups by its percentiles. The test for trend of survival estimates indicated that higher IA levels increased risk of OD, especially early on (Wilcoxon test, p = 0.03; log-rank test, p = 0.07) (Figure 4a). The 4 groups of IA also showed the same trend (Wilcoxon test, p = 0.04; log-rank test, p = 0.12) (Figure 4b).

(a) 3 - IA groups (b) 4 - IA groups

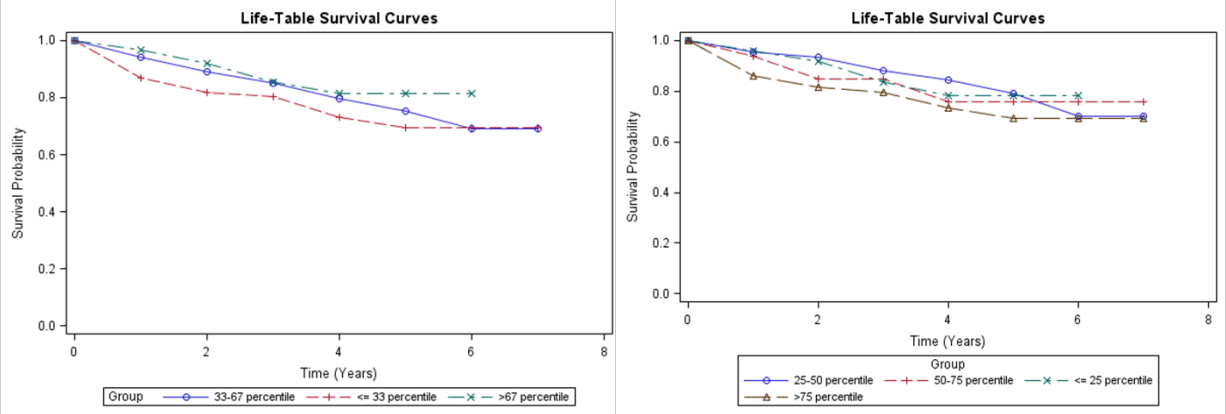
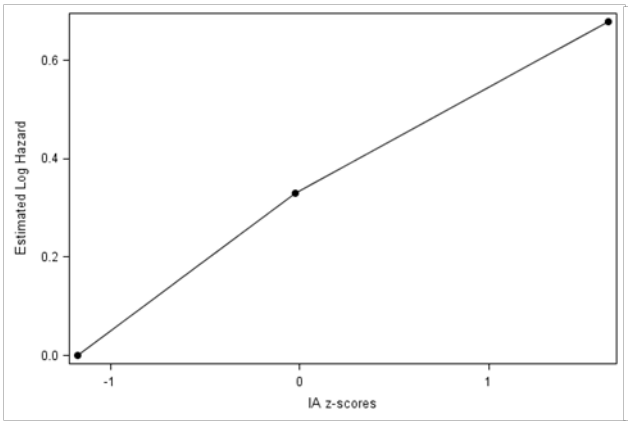


Figure 4. OD-free survival curves for 3 and 4- level representation of IA

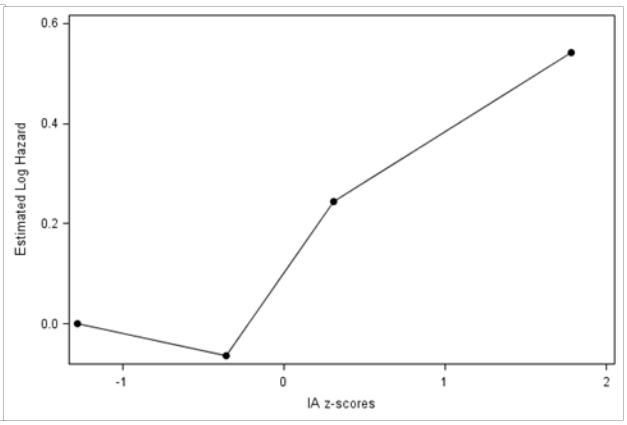
The same trend can be observed from the graph of the log hazard ratios for the IA groups. Indeed, Figure 5 clearly indicates that offspring with higher IA tend to have higher estimated hazard rates. For the trichotomous representation of the IA variable, the hazard ratios of the two high IA groups were respectively 1.39 and 1.97 as compared to the low IA group. For the 4-cateory IA variable, the hazard ratios of the three high IA groups were 0.94, 1.28 and 1.72, respectively. Discretizing IA into 5 groups or even more, we observed that some departures from

increasing relationships of hazard ratios (Figure 5c). Unfortunately with the available sample size we were unable to identify any systematic non-linear trends.

(a) 3 - IA groups



(b) 4 - IA groups



(c) 5 - IA groups

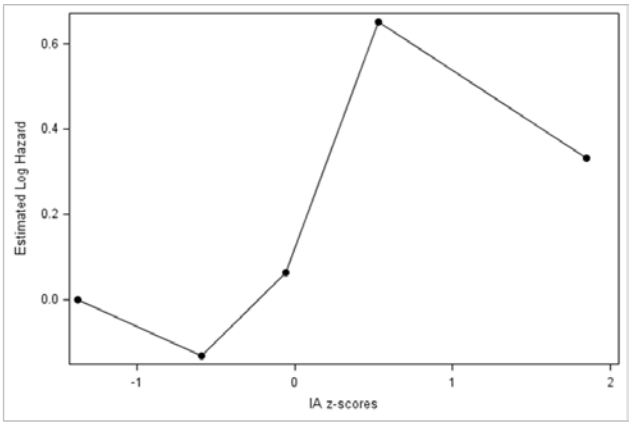


Figure 5. Estimated log hazard ratios for 3, 4- and 5-level representation of IA

The non-monotonicity of the hazard ratios observed in Figure 5c combined with the low sample size (47 events overall) seems to be the primary reason for non-significance of **t**he

continuous IA score in the univariate proportional hazards model (HR = 1.19, 95% CI: 0.89 to 1.60, p = 0.25). The effect of the continuous IA score (either *z*-score or in its original scale) remained non-significant in the three age subgroups.

4.3 MULTIVARIABLE MODELS

Using proportional hazards models for discrete time to OD, we built the following three multivariate models for further investigation of the adjusted effect of IA: 1) based on demographic and historical covariates; 2) based on all offspring-level covariates; and 3) based on offspring- and proband-level covariates. The primary variable of interest, IA, was intentionally excluded from this model building step. Instead, the built models were used in the next section for evaluating the adjusted effect of IA on the risk of OD.

Analyzing individual offspring-level covariates in the discrete survival analysis setting, we found that more mature pubertal status (HR = 1.35, 95% CI: 1.00 to 1.83, p = 0.04), behavioral disorder (HR = 2.51, 95% CI: 1.32 to 4.77, p = 0.005), higher self-reported depression symptoms (HR = 1.29, 95% CI: 1.02 to 1.62, p = 0.03), and more negative life events (HR = 1.27, 95% CI: 0.96 to 1.70, p = 0.10) were univariately associated with higher risk of OD (Table 8). Site was also associated with OD (HR = 0.47 (Pittsburgh vs. New York), 95% CI: 0.26 to 0.87, p = 0.02) with participants in Pittsburgh having lower risk of depression.

Table 8. Univariate effects of individual offspring-level variables

Offspring variables	Hazard ratio	95% CI	χ^2_1	p
Age	1.04	[0.97, 1.11]	1.33	0.25
Female	1.03	[0.58, 1.84]	0.01	0.92
Caucasian	0.79	[0.43, 1.47]	0.54	0.46
Hispanic ethnicity	1.99	[0.78, 5.05]	2.07	0.15
Puberty	1.35	[1.00, 1.83]	4.29	0.04
Pittsburgh site	0.47	[0.26, 0.87]	5.83	0.02
DSM-IV Diagnoses				
Anxiety disorder	1.14	[0.55, 2.37]	0.13	0.72
Behavior disorder	2.51	[1.32, 4.77]	7.95	0.005
Antisocial disorder	1.87	[0.39, 8.82]	0.62	0.43
Post-traumatic stress disorder	1.61	[0.50, 5.21]	0.63	0.42
Clinical Characteristics				
Impulsive aggression*	1.19	[0.89, 1.60]	1.34	0.25
Impulsivity*	1.12	[0.85, 1.48]	0.52	0.43
Aggression	1.03	[0.98, 1.08]	1.16	0.26
Self-reported depressive symptoms *	1.29	[1.02, 1.62]	4.56	0.03
Negative life events*	1.27	[0.96, 1.70]	2.71	0.10
Hopelessness*	1.20	[0.96, 1.51]	2.56	0.11
Non-suicidal self-injury behavior	3.14	[0.75, 3.24]	2.44	0.12
Alcohol/substance abuse	0.87	[0.27, 2.81]	0.06	0.81
Physical/sexual abuse	1.18	[0.50, 2.79]	0.14	0.71
Childhood anxiety	1.01	[0.98, 1.04]	0.42	0.52
Adaptability and cohesion	1.00	[0.96, 1.04]	0.005	0.94
Dichotomized IA	2.00	[1.13,3.55]	5.64	0.02

*Standardized *z*-score;

Dichotomized IA indicated the high and low IA groups.

Using $\alpha = 0.1$ as the selection criterion, 5 variables, site, puberty, negative life event, behavior disorder, and self-reported depressive symptoms, were eligible to enter the multivariable regression model. From these, only site and puberty were significant at the level of 0.05, in the multivariable model based on demographic or historical variables (Model 1, Table 9). No significant interactions were found. The final multivariable model based on all offspring-level variables included behavior disorder, puberty and site (Model 2, Table 9).

Table 9. Multivariable models based on offspring-level covariates

	Hazard ratio	95% CI	Z	p
Model 1: demographic/historical variables				
Pittsburgh site	0.49	[0.26, 0.92]	-2.20	0.03
Puberty	1.38	[1.03, 1.84]	2.19	0.03
Model 2: offspring variables				
Behavior disorder	4.31	[2.12, 8.81]	4.04	<0.001
Pittsburgh site	0.41	[0.21,0.79]	-2.67	0.01
Puberty	1.63	[1.20,2.22]	3.13	0.002

Analyzing individual proband-level variables in the discrete survival analysis setting, we found that proband anxiety disorder (HR = 1.79, 95% CI: 0.91 to 3.52, p = 0.09), alcohol or substance abuse (HR = 0.48, 95% CI: 0.27 to 0.87, p = 0.02), borderline personality disorder (HR = 1.88, 95% CI: 0.99 to 3.59, p = 0.05), self-reported depression symptoms (HR = 1.03, 95% CI: 1.01 to 1.05, p = 0.01), and interviewer-rated depression symptoms (HR = 1.02, 95% CI: 1.00 to 1.05, p = 0.06) were significant at $\alpha = 0.1$ (Table 10).

Table 10. Univariate effects of individual proband-level variables

Proband variable	Hazard ratio	95% CI	χ^2_1	p
Age	1.02	[0.98, 1.06]	0.99	0.32
Female	0.96	[0.43, 2.14]	0.01	0.91
Caucasian	0,73	[0.39, 1.37]	0.97	0.33
Hispanic ethnicity	1.55	[0.55, 4.36]	0.70	0.40
SES	1.00	[0.96, 1.04]	0.02	0.88
Suicide attempt	1.11	[0.62, 1.99]	0.12	0.73
Non-suicidal self-injury behavior	0.70	[0.31, 1.58]	0.74	0.39
Depression	0.64	[0.33, 1.23]	1.80	0.18
Bipolar	1.35	[0.70, 2.61]	0.82	0.37
Anxiety disorder	1.79	[0.91, 3.52]	2.84	0.09
Eating disorder	0.83	[0.30, 2.31]	0.13	0.72
Borderline	1.88	[0.99, 3.59]	3.72	0.05
Antisocial	0.98	[0.30, 3.17]	0.001	0.98
Post-traumatic stress disorder	1.20	[0.66, 2.20]	0.35	0.55
Alcohol/substance abuse	0.48	[0.27, 0.87]	5.76	0.02
Physical/sexual abuse	1.49	[0.54, 4.10]	0.59	0.44
Interview-rated depressive symptoms	1.02	[1.00, 1.05]	3.61	0.06
Self-reported depressive symptoms	1.03	[1.01, 1.05]	7.18	0.01
Hopelessness	1.02	[0.97, 1.07]	0.85	0.36
Impulsive aggression	1.01	[0.99, 1.04]	1.83	0.18
Impulsivity	1.01	[0.99, 1.02]	0.92	0.34
Aggression	0.99	[0.94, 1.04]	0.19	0.67
Highest lifetime suicidal ideation	1.02	[0.99, 1.05]	2.42	0.12

SES: socio-economic status.

Adding the five significant proband variables to the offspring model yielded a final model including offspring puberty, offspring behavior disorder, proband anxiety disorder, proband alcohol/substance abuse and site (Table 11). Some of the borderline significant variables in the final model were kept because of their practical importance and/or significance after later inclusion of the IA variable. No significant interactions among offspring and proband variables were detected.

Table 11. Multivariable model based on both offspring and proband variables

Model 3	Hazard ratio	95% CI	z	p
Behavior disorder	3.78	[1.74, 8.21]	3.36	<0.001
Puberty	1.72	[1.23, 2.40]	3.15	0.002
Pittsburgh site	0.51	[0.25, 1.05]	-1.82	0.07
Proband anxiety disorder	2.07	[0.98, 4.38]	1.91	0.06
Proband alcohol/substance abuse	0.48	[0.26, 0.92]	-2.23	0.03

4.4 EFFECT OF IA ADJUSTING FOR OTHER COVARIATES

We used the multivariable models described in the previous section to evaluate the adjusted effect of IA. In the context of Model 1, controlling for demographic or historical offspring-level variables (puberty and site), high IA group was significantly related to high risk of OD (HR = 2.28, 95% CI: 1.27 to 4.11, p = 0.01) (Table 12). The magnitude and statistical effect of IA effect was alleviated (HR = 1.77, 95% CI: 0.95 to 3.29, p = 0.09) after controlling for all offspring level variables (Model 2, which includes behavior disorder, site and puberty); However, it regained both magnitude and significance after controlling for both offspring and probands variables in Model 3 (HR = 2.06, 95% CI: 1.05 to 4.05, p = 0.04). No significant interactions among the variables were detected. Adjustment for the correlation between responses of the siblings (offspring of the same proband) did not affect the results substantially.

Table 12. Estimated hazard ratios of IA adjusting for other covariates

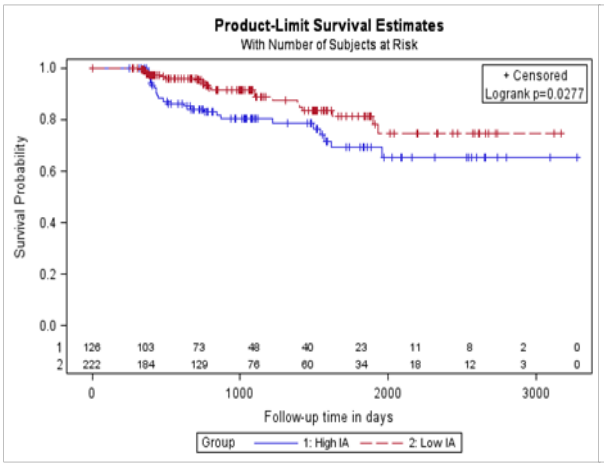
	w/o adjusting for proband clusters		w/ adjusting for proband clusters	
	Hazard ratio	p	Hazard ratio	p
Model 1: demographic/historical variables				
Dichotomized IA	2.28	0.01	2.29	0.01
Pittsburgh Site	0.44	0.01	0.45	0.02
Puberty	1.43	0.02	1.42	0.02
Model 2: offspring variables				
Dichotomized IA	1.77	0.07	1.77	0.09
Pittsburgh Site	0.40	0.01	0.40	0.01
Puberty	1.65	0.003	1.64	0.002
Behavior disorder	3.47	0.001	3.47	0.001
Model 3: offspring and probands variables				
Dichotomized IA	2.07	0.02	2.06	0.04
Behavior disorder	2.93	0.005	2.93	0.008
Puberty	1.81	0.001	1.79	0.001
Pittsburgh site	0.51	0.048	0.51	0.07
Proband anxiety disorder	2.22	0.03	2.21	0.04
Proband alcohol/substance abuse	0.42	0.01	0.43	0.01

4.5 ANALYSIS OF CONTINUOUS TIME TO EVENT

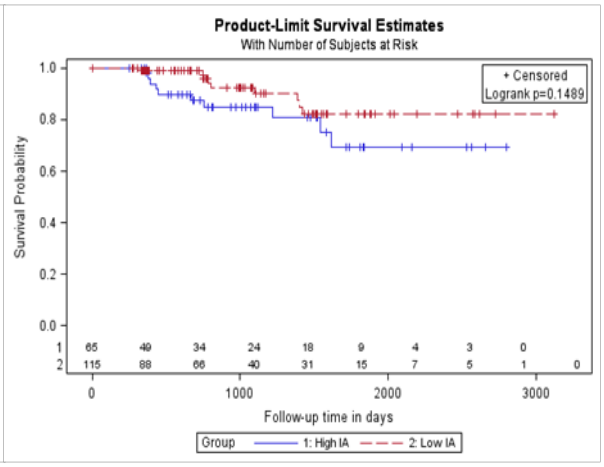
We checked the consistency of our findings with the results of continuous-time survival analysis (using standard Cox model, Wilcoxon and log-rank test). As we discussed in Section 4.2, the optimal dichotomization of IA using the Contal and O'Quigley method led to the same IA cutpoint for continuous time (days to OD) as for discrete time (years to OD). Thus, we considered the same dichotomized IA in the continuous time to event analysis. The Cox models showed similar, but less statistically significant, estimate of the univariate effect of dichotomized

IA (HR = 1.88, 95% CI: 1.06 to 3.35, p = 0.03) (Table 13). OD-free survival experience of high IA level was worse, although not statistically significant, than that of low IA levels in all age groups 10 - 13, 14 - 17 and 18 - 25 years old (Wilcoxon test, p = 0.08, 0.07, and 0.25, respectively; log-rank test, p = 0.15, 0.19, and 0.32, respectively) (Figures 6b, 6c, 6d).

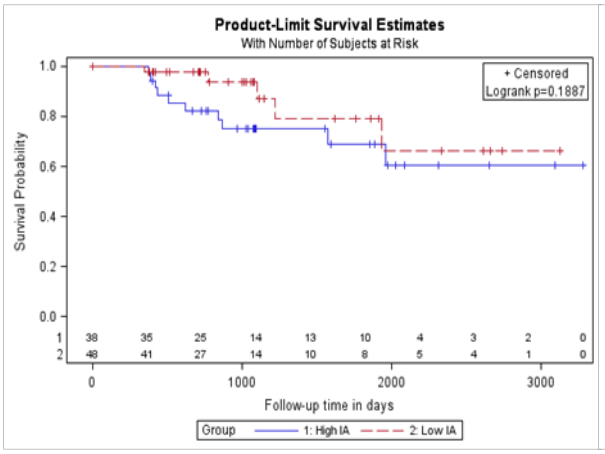
(a) 348 offspring



(b) 10-13 years



(c) 14-17 years



(d) 18-25 years

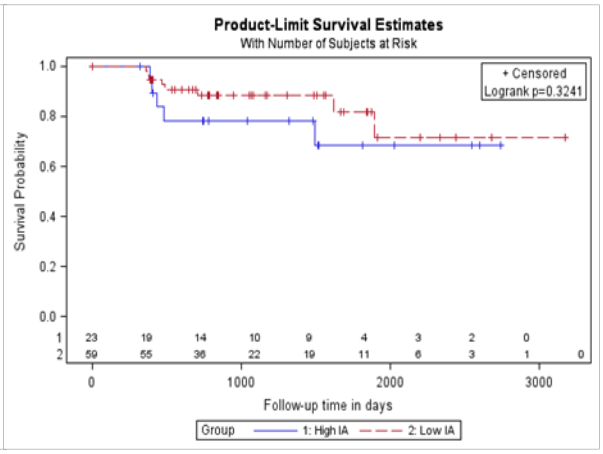


Figure 6. OD-free survival curves for high and low IA levels (continuous time)

Table 13 reports the relationship of each offspring variables to OD in the context of the Cox proportional hazards model. Three offspring variables, puberty (HR = 1.31, 95% CI: 0.97 to 1.78, p = 0.06), behavior disorder (HR = 2.35, 95% CI: 1.24 to 4.45, p = 0.01) and self-reported depression symptoms (HR = 1.26, 95% CI: 1.00 to 1.59, p = 0.05) were significant at $\alpha = 0.1$. Site was also significantly related to OD (p = 0.02) with participants followed in Pittsburgh having lower risk of depression. Five proband variables were significant at $\alpha = 0.1$, namely anxiety disorder (HR = 1.80, 95% CI: 0.92 to 3.54, p = 0.09), alcohol or substance abuse (HR = 0.49, 95% CI: 0.27 to 0.89, p = 0.02), borderline personality disorder (HR = 1.73, 95% CI: 0.91 to 3.29, p = 0.10), self-reported depression symptoms (HR = 1.03, 95% CI: 1.01 to 1.05, p = 0.02), and interview-rated depression symptoms (HR = 1.02, 95% CI: 1.02 to 1.05, p = 0.10).

The results of the evaluation of the adjusted effect of IA in the continuous time setting closely agree with the results for discrete time to event analysis previously described. Namely, high IA was significantly associated with higher risk of OD in the demographic/historical model (HR = 2.01, 95% CI: 1.13 to 3.58, p = 0.02). In the model built on all significant offspring-level covariates including behavior disorder and puberty, and site, IA had a hazard ratio of 1.65 (95% CI: 0.88 to 3.08, p = 0.12). In the most comprehensive model built on both offspring and proband-level covariates, IA had regained its original strength (HR = 1.92, 95% CI: 1.02 to 3.64, p = 0.04) after adjusting for site, behavior disorder, puberty, proband anxiety disorder, proband alcohol or substance abuse. No significant interactions between variables were found.

Table 13. Univariate effects of individual offspring-level variables (continuous time)

Offspring variables	Hazard ratio	95% CI	χ^2_1	p
Age	1.03	[0.97, 1.11]	0.90	0.34
Female	1.04	[0.58, 1.86]	0.02	0.89
Christian	0.81	[0.44, 1.50]	0.44	0.51
Hispanic ethnicity	2.04	[0.80, 5.17]	2.24	0.14
Puberty	1.31	[0.97, 1.78]	3.64	0.06
Pittsburgh site	0.48	[0.27, 0.89]	5.45	0.02
DSM-IV diagnoses				
Anxiety disorder	1.07	[0.52, 2.21]	0.03	0.86
Behavior disorder	2.35	[1.24, 4.45]	6.85	0.01
Antisocial disorder	1.81	[0.39, 8.52]	0.57	0.45
Post-traumatic stress disorder	1.35	[0.42, 4.38]	0.61	0.61
Clinical characteristics				
Impulsive aggression*	1.14	[0.85, 1.53]	0.74	0.39
Impulsivity*	1.10	[0.83, 1.46]	0.35	0.51
Aggression	1.02	[0.98, 1.07]	0.81	0.33
Self-reported depressive symptoms*	1.26	[1.00, 1.59]	3.75	0.05
Negative life events*	1.23	[0.93, 1.64]	2.10	0.15
Hopelessness*	1.18	[0.94, 1.49]	2.13	0.15
Non-suicidal self-injury behavior	3.02	[0.71, 12.83]	2.25	0.13
Alcohol/substance abuse	0.80	[0.25, 2.58]	0.14	0.71
Physical/sexual Abuse	1.15	[0.49, 2.73]	0.10	0.75
Childhood anxiety	1.01	[0.98, 1.04]	0.26	0.61
Adaptability and cohesion	1.00	[0.96, 1.04]	0.02	0.90
Dichotomized IA	1.88	[1.06, 3.35]	4.69	0.03

*Standardized *z*-score.

Table 14. The multivariable models (continuous time)

	Hazard ratio	95% CI	χ^2_1	p
Model 1: demographic/historical variables				
Dichotomized IA	2.01	[1.13, 3.58]	5.61	0.02
Pittsburgh site	0.45	[0.25, 0.83]	6.50	0.02
Model 2: all offspring variables				
Dichotomized IA	1.65	[0.88, 3.08]	2.46	0.12
Behavior disorder	2.96	[1.43, 6.10]	8.61	0.003
Puberty	1.58	[1.14, 2.19]	7.53	0.01
Pittsburgh site	0.43	[0.23, 0.81]	6.91	0.01
Model 3: offspring and proband variables				
Dichotomized IA	1.92	[1.02, 3.64]	4.03	0.04
Behavior disorder	2.46	[1.17, 5.15]	5.66	0.02
Puberty	1.72	[1.21, 2.46]	9.08	0.003
Pittsburgh site	0.57	[0.29, 1.10]	2.83	0.09
Proband anxiety disorder	2.17	[1.05, 4.47]	4.43	0.04
Proband alcohol/substance abuse	0.42	[0.22, 0.82]	6.52	0.01

The weaker magnitude and statistical significance of the effect of IA in the continuous time-to-event setting was likely due to by a more pronounced non-proportionality of hazards on the continuous time scale. Figure 7a indicates that there was a substantial non-proportionality of the empirical estimates of the first-days hazards, while discrete-time estimates of the first-years hazards were free of these problems with two IA groups being represented by relatively parallel lines (Figure 7b).

(a) Continuous time (days) (b) Discrete time (years)

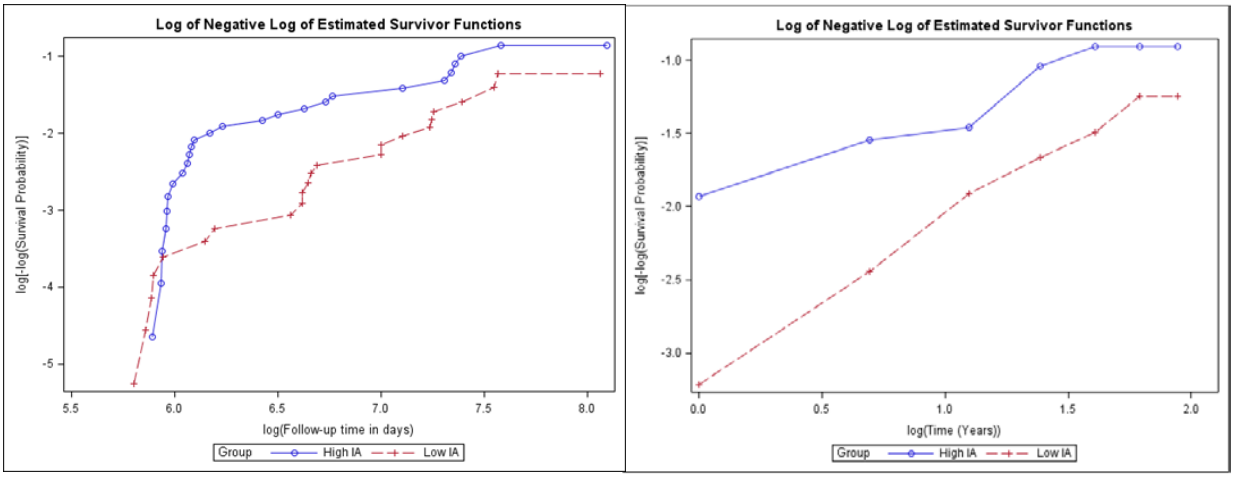


Figure 7. Log of the cumulative hazard rates for high and low IA levels

4.6 SENSITIVITY/SECONDARY ANALYSES

First we evaluated sensitivity of our results with respect to the imputed values. Analyses were repeated without 26 offspring with imputed baseline IA scores. We found that the estimates from models 1-3 fitted using the 322 offspring who had recorded baseline IA scores were very similar to those from the 348 offspring with IA scores imputed (Table 15 vs. Table 12).

We also verified that our results were not sensitive to the form of the only continuous variable included in models 1-3, namely, puberty. The estimates for the other effects in models 1-3 were similar if the puberty variable was dichotomized at the median to indicate mature or non-mature statuses.

Table 15. Multivariable estimates after exclusion of previously imputed observations

	Hazard ratio	p
Dichotomized IA (univariate)	2.00	0.02
Model 1: demographic/historical variables		
Dichotomized IA	2.26	0.004
Puberty	1.40	0.03
Pittsburgh site	0.48	0.01
Model 2: offspring variables		
Dichotomized IA	1.73	0.09
Behavior disorder	3.64	<0.001
Puberty	1.62	0.005
Pittsburgh site	0.42	0.01
Model 3: offspring and proband variables		
Dichotomized IA	2.00	0.05
Behavior disorder	3.12	0.005
Puberty	1.75	0.002
Pittsburgh site	0.54	0.09
Proband anxiety disorder	2.01	0.07
Proband alcohol/substance abuse	0.42	0.01

We also verified the sensitivity of our results with respect to the presence of multiple offspring of the same proband. In the models estimated on the subset of data with 1 offspring per proband, participants with high IA level conveyed a hazard ratio of 1.77 (95% CI: 0.99 to 3.18, p = 0.06) univariately. In the demographic/historical model 1 adjusting for site, high IA group was significant associated with high risk of OD (HR = 1.86, 95% CI: 1.04 to 3.33, p = 0.04). In the context of model 2 or 3, after adjusting other offspring and proband covariates, the magnitude of the IA effect was similar, albeit not statistically significant. The loss of the statistical significance in some models could be caused by the smaller sample size in the 1-offspring per proband analyses.

In one of the secondary analyses we evaluated the dose-response type of relationship of baseline level of IA and the risk of OD. Although the estimate of ordinal 3-category IA effect in

the most comprehensive model (model 3) was not statistically significant (HR = 1.4 per difference between adjacent IA categories, 95% CI: 0.92 to 2.14, p = 0.12) (Table 16), its magnitude agreed with the univariate results (HR = 2.00, 95% CI: 1.13 to 3.55). The hazard ratios for the other covariates in the model did not change substantially from the estimates attained with the dichotomized IA.

Table 16. Adjusted estimates for the ordinal (3-level) IA variable

	Hazard ratio	95% CI	p
IA (3 levels)	1.40	[0.92,2.14]	0.12
Behavior disorder	3.10	[1.34,7.18]	0.01
Puberty	1.73	[1.23,2.44]	0.002
Pittsburgh site	0.50	[0.24,1.05]	0.07
Proband anxiety disorder	2.22	[1.03,4.77]	0.04
Proband alcohol/substance abuse	0.44	[0.23,0.85]	0.01

We also examined the relationship between IA and the most significant risk factor we identified - behavior disorder. Behavior disorder was closely related to high IA, with the rate of behavior disorder in the high IA group being significantly greater than in the lower IA group (26.5% vs. 9.4%, $\chi^2_1 = 16.92$, $p < 0.001$). ROC indicated a moderate association of continuous IA scores with behavior disorder (area under the curve [AUC] = 0.68, 95% CI: 0.57 to 0.75) (Figure 8). The probability (IA *z*-score > 0.338 | behavior disorder) = 0.68 and probability (IA *z*-score > 0.338 | no behavior disorder) = 0.38.

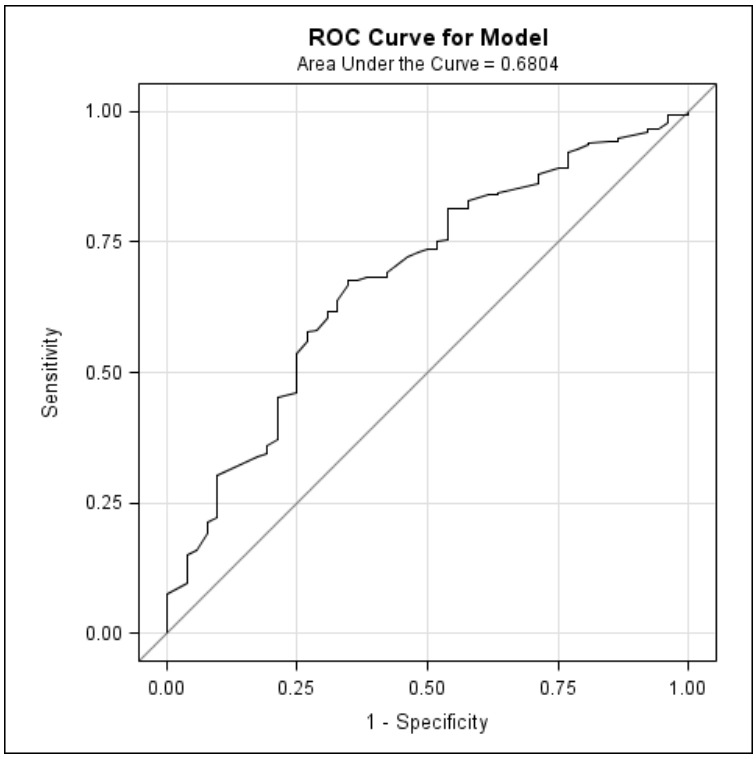


Figure 8. ROC curve for IA as a predictor of behavior disorder

Finally, although in this dataset we never observed its significant effects on the risk of OD, sex of participant was considered an important factor which could contribute to risk of depression as well as affect the effects of other factors. Thus, we assessed the effect of IA on OD in both sexes and found some, albeit non-statistically significant, indication that the IA effect could be more pronounced for female than males. The hazard ratio of IA to OD in females was 2.86 (95% CI: 1.16 to 7.05, p = 0.02) as compared to that of 1.50 (95% CI: 0.71 to 3.02, p = 0.29) in males. The corresponding interaction was not statistically significant. In the models stratified by gender, IA and other variables had estimated effects similar to those in the originally built models.

5.0 DISCUSSION AND CONCLUSION

In recent years, the possible importance of impulsive aggression as a risk factor for depression has been increasingly gaining attention. Previous FAMPATH reports found that there was an association between impulsive aggression and earlier onset of depressive disorder, but it was not clear if depression led to higher impulsive aggression or vice versa. In this study, we examined whether impulsive aggression is a predictor of the future onset of depressive disorders in youth. The hazard ratio of dichotomized IA, either univariately or after adjustment for other covariates, was close to 2, indicating that the risk of depression onset for youth with high IA level was approximately twice as that of the low IA level. We also found some evidence of a dose-response type of relationship between impulsive aggression and onset of depression, in the sense that incremental increase of IA level within high/and low IA groups was also associated with increasing chances of OD. Our findings are consistent with a number of previous studies showing that attentional difficulties, impulsivity, and aggression are common precursors of early-onset depression (Chronis-Tuscano et al., 2010; Jaffee et al., 2002).

According to our findings the levels of impulsive aggression can be used for updating the risk of depression onset by comparing the reported scores to the middle of the instrument scale. The scores that are higher than the middle of the scale are associated with approximately two-fold risk of future onset on depression at any given of the next 6 years. Interestingly, this recipe

works for both two instrument scales used in this study, and the two-fold increase in risk provides good approximation regardless of other covariate information.

When building multivariate models for the future depression onset, we found several offspring and probands risk factors related to the offspring depression onset. The offspring risk factors were behavior disorder, puberty, and site where the participants were recruited; the proband risk factors were anxiety disorder and substance abuse. In our dataset behavior disorder is the most significant risk factor that increases the risk of future depression onset by three to four times. Impulsive aggression and behavior disorder are naturally but not perfectly related. As a result, after adjusting for behavior disorder in the offspring covariate models the magnitude and statistical significance of the effect of impulsive aggression was alleviated. Puberty has long been implicated in the developmental course of early-onset depressive disorders, and in the development period of adolescence. Our study observed that risk of depression onset was higher in the mature youth. Increased risk of depression onset for the youth with known behavior disorder was in part explained by the proband-level risk factors of anxiety disorder and alcohol/substance abuse. Adjusting for these risk factors the effect of the offspring behavior disorder reduced and the effect of impulsive aggression regained the magnitude and statistical significance. These findings highlight the importance of taking familial factors into offspring depression intervention.

In perspective our findings could also help develop a better understanding of the risk of suicidal behavior. Previous studies reported that impulsive aggression and depression are related to suicidal risk (Mann et al., 2005; Melhem et al., 2007), while our study showed that impulsive aggression also increased the risk for the onset of depression. It is also possible that onset of depression affects the levels of impulsive aggression; correspondingly investigation is beyond

the scope of the current projects. Our findings combined with future investigation of the effect of depression onset on levels of impulsive aggression are likely to be instrumental for understanding the interrelationship among risk factors for both depression and suicidal behavior.

In this project we used data from one of only a few longitudinal studies to examine the effect of impulsive aggression on the onset of mood disorders, and perhaps the only high-risk family study to do so. However, some limitation of the study prevented more detailed analyses and to a certain degree could have affected the generalizability of the obtained results. First, impulsive aggression was only assessed by self-report and not by direct interview. Second, probands were a referred sample instead of communities-recruited. Third, the studied cohort had a relatively low incidence of depression resulting in only 47 depression onsets in an 8-year period. This prevented better understanding of the dose-response type of relationship between the baseline levels of impulsive aggression and depression onset, as well as prohibited conclusive analyses of possible interactions of effects of impulsive aggression with secondary factors (e.g., gender). More work in intervention and prevention research would be needed to answer these questions.

In conclusion, we found that impulsive aggression is an important risk factor for future depression onset, and its effect is reflected in other measurements. This knowledge will help improve understanding of risk of early-onset of depression, thereby facilitating treatment of those at risk for depression or even suicidal behavior, and developing prevention strategies targeted at high-risk group.

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