ORIGINAL CONTRIBUTION

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The relation between the age at diagnosis of problem behaviors related to aggression and distal outcomes in Swedish children

Ian Campbell[1] · Sebastian Lundstrom[2] · Hendrik Larsson[3] · Paul Lichtenstein[3] · Gitta Lubke[1]

Abstract

Severe childhood aggressive behaviors are known to predict negative outcomes later in life; however, little is known about the effect of when in childhood aggression problems are diagnosed. While an earlier first diagnosis of problematic aggressive behavior might be associated with increased severity and, thus, worse outcomes, it is also possible that an earlier diagnosis affords an earlier start of treatment programs or indicates that greater attention is being paid to behavioral problems, thus resulting in attenuation of the severity of childhood aggression's impact on distal outcomes. The current study analyzed data from the population-based Swedish Data Registries, which include data on all children formally diagnosed by the Swedish medical system with a wide range of aggression problems between ages 8 and 18 ($N = 5816$) during the years 1987–2013, along with a matched control. Time-to-event analyses investigated whether the age at time of diagnosis affects later life outcomes while controlling for relevant confounders. Results show that for both boys and girls, those with a later diagnosis had lower average incomes (regression coefficient $b = -0.055$, $p < 0.005$) and a higher probability of having a criminal record (odds ratio 1.126, $p < 0.005$) than children with earlier diagnoses. The effect on suicide attempts was not significant after correcting for multiple testing (odds ratio 1.264, $p = 0.016$). Grade score was not significantly affected. The results warrant further research concerning the potential advantage of earlier diagnoses, especially concerning generalizability beyond the Swedish population.

Keywords Childhood aggression · Conduct disorder · Time-to-event analysis · Swedish data registry

Introduction

Childhood aggression is a serious problem for society at large as well as for the individual. It is one of the most common forms of childhood maladjustment [1–3]. Aggression inflicts a large personal, psychological, and financial burden on the affected individuals, their friends and families, and

✉ Gitta Lubke
glubke@nd.edu

1   Department of Psychology, University of Notre Dame, Notre Dame, USA

2   Institute of Neuroscience and Physiology, Centre for Ethics Law and Mental Health, Gillberg Neuropsychiatry Centre, University of Gothenburg, Gothenburg, Sweden

3   Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

society as a whole [4–6]. Aggressive children often have worse outcomes later in life, including poorer health outcomes [7, 8], worse performance and greater peer rejection in school [9, 10], less earning potential later in life [11] and higher risk of criminal behavior [12, 13]. While it is known that childhood aggression predicts worse outcomes later in life, it is unclear whether the age at which a child is first diagnosed with problem behaviors related to aggression impacts societal and individual outcomes. An earlier diagnosis could reflect more severe problem behaviors, in which case outcomes are expected to be more severe [14, 15]. However, it is also possible that an earlier diagnosis affords earlier access to treatment or that it results in an overall greater level of attention being paid to a child's behavioral issues, potentially leading to an attenuation of the severity of outcomes. The current study seeks to address this question by examining the effect of when a child is first diagnosed with an aggressive behavior problem on outcomes later in life.

As a first attempt to address this question, this study considers a range of diagnoses related to childhood aggression

and conduct problems to encompass a broad definition of aggression. Some researchers have limited definitions of persistent aggression problems to diagnoses of conduct disorder (CD) or oppositional defiant disorder (ODD) [16]. According to both the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Statistical Classification of Diseases and Related Health Problems (ICD), CD's defining characteristic is aggressive behavior that results in "significant impairment in social, academic, or occupational functioning" and violation of the fundamental rights of others or societal norms or rules [17, 18]. There is also a history in the literature of viewing ODD as a milder form of aggressive problem behavior and, thus, a potential precursor to CD [19]. Meanwhile, others have taken a more broad definition of aggressive behavior, to include not only diagnoses of CD and ODD, but also other behaviors, both physical and relational, that aim at hurting or harming others [5, 10, 20].

Employing a definition of problematic aggressive behavior that is broader than a CD or ODD diagnosis has both advantages and limitations. A strict definition of only a CD or ODD diagnosis would ideally increase consistency and focus research on cases that are severe enough to reach these clinical standards. However, Loeber, Burke, Lahey, Winters, and Zera [21] found that there is often disagreement among clinicians regarding weather some symptoms are part of ODD or CD and that CD exhibits clear heterogeneity. This might explain why these researchers found that estimates of the prevalence of CD in children range from 2 to 16% depending on the specific population under study as well as the particular sampling method employed. Rowe, Costello, Angold, Copeland, and Maughan [19] also found that treating ODD simply as a milder case of CD ignores important differences in the symptoms and subtypes of both conditions. By implementing a broader definition of aggressive behavior than a CD or ODD diagnosis, researchers have been able to avoid the potential inconsistencies in diagnosing these two specific conditions as well as focus on distinctions between physical and verbal aggression and include other behaviors that can be considered aggressive in nature, such as indirect aggression, disruptive actions, and troublesome behaviors [5, 10, 20].

Given the heterogeneity of CD and ODD [19, 21] and the ability of a broader definition to capture a wider range of aggressive behaviors and conduct problems, a more comprehensive definition seemed appropriate for this initial investigation into the effects of the timing of the first diagnosis of problematic behaviors related to aggression. In particular, a first diagnosis was recorded when a child received an initial diagnosis of CD, ODD, other or unspecified conduct problems, or adjustment disorder with conduct or emotional disturbances. This broad definition permits assessing the impact

of aggressive behaviors and conduct problems beyond those of CD or ODD.

It is well known that the expression of aggressive behaviors differs for boys and girls [5, 11]. There is typically consensus that overall boys exhibit more aggression than girls [22, 23] and CD diagnosis rates are higher in boys (13.2%) than in girls (3.7%) [19]. However, some studies have found that girls exhibit higher levels of relational aggression than boys [24], but other studies have failed to find this difference [25–27]. Wildeboer et al. [10] and others [28] recommend studying aggression separately in boys and girls to prevent the possibility of a Simpson's paradox from obscuring the true direction of effects. In accordance with this suggestion, the analyses of childhood aggression in this study were carried out separately for boys and girls.

In this study, population-based Swedish Data Registries were investigated to assess the potential effects of the timing of an initial diagnosis on later life outcomes for boys and girls. The Swedish Data Registries contain information for the entire population of Sweden, recorded each year on a large number of variables. All boys and girls who are diagnosed with an aggression problem are recorded in these registries, along with relevant covariates and distal outcome variables. The healthcare system in Sweden is universal and government funded, and because these children were identified by the healthcare system as having an aggression diagnosis, it is reasonable to assume that when they were diagnosed with an aggression problem, these children were also given access to different potential treatment options, or at least doctor recommendations on how to address the child's aggressive behavior. However, the Swedish data registries contain information neither on the potential treatment options offered to children at the time of their diagnosis nor on the success rates of different treatment plans. Therefore, this study is limited to consider the impact of the time of initial diagnosis, while understanding that for some children this could also be the time of initial access to treatment options.

This study's main aim was to investigate the effects of age of first diagnosis for boys and girls on four important areas of societal life: mental health, educational performance, economic success, and criminal activity. The selected outcomes were suicide risk, school performance, personal income, and criminal record. In a first set of analyses we compare individuals with a diagnosis and undiagnosed controls with respect to associations of these four outcomes, while controlling for potentially relevant background variables, including neighborhood deprivation, mothers' education and criminal record, and family income. Next, time-to-event analysis [29] was used to investigate whether the age of initial diagnosis mediates the effects of the background variables on the four outcomes. This is the first time-to-event analysis to examine the effects of the timing of an initial diagnosis on

later life outcomes. More severe cases of aggression might be detected at an earlier age and, thus, might also present with more severe outcomes. If earlier diagnosis is predictive of less severe outcomes, then such a result would support efforts to strive for early detection of aggression problems.

Methods

Data

Similar to previous population registry studies [30–33], several longitudinal population-based registries in Sweden were combined using a unique personal identification number, which renders linkage across registers possible, to obtain a large collection of variables. Age at first diagnosis was defined as the age of a subject when he or she received an initial inpatient or outpatient medical procedure which resulted in an assigned ICD code for problematic aggressive behavior. Due to data availability, the year range considered in this study was between 1987 and 2013. The ICD-9 code of 312 was used to define aggressive behavior from 1987 to 1996, and the ICD-10 codes F43.24, F43.25, F90.1, F91.1–9, and, F92.0–9 were used from 1997 to 2013.

Exposure

In the entire population of Sweden, between 1987 and 2013, a total of 17,044 subjects were recorded with an aggression diagnosis. This study focused on the 5816 case subjects who were diagnosed between the ages of 8 and 18 and who had reached the age of 18 by the end of 2013. Diagnoses that occur before the age of 8 may not be reliable, and those that happen after age of 18 concern adult, not childhood, aggression [34, 35]. All case subjects included in the final analyses were born between 1987 and 1995. All subjects needed to be at least 18 years old by 2013, so information on their outcome variables would be available. Controls were defined as subjects without a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) or any of the aggressive problem diagnoses mentioned earlier. Matching was done based on geographic region, age, and sex. The total final sample size was $N = 11{,}632$ (6462 boys and 5170 girls), with an equal number of cases and controls.

We investigated the utility of a large number of potentially relevant covariates and distal outcomes in an exploratory partition of the data (see "Exploratory Analyses" and Supplemental Material for more detail). The covariates and outcomes that were selected in the exploratory analyses are described in more detail below.

Covariates

The selected covariates were the subjects' mother's maximum education level achieved as well as her criminal conviction history, the subjects' average Neighborhood Deprivation score and average Family Income, and whether or not the subject also had an ADHD or ODD diagnosis.

Mother's maximum education level was based on a 7-point scale, with 1: primary school < 9 years, 2: primary school 9 years, 3: upper secondary school ≤ 2 years, 4: upper secondary school > 2 years, 5: post secondary school < 3 years, 6: post secondary school ≥ 3 years, and 7: postgraduate education. Mother's criminal conviction was scored as 1 if the mother had any criminal convictions and 0 otherwise. The subject's Neighborhood Deprivation (ND) score [36] is a composite score of eight deprivation indicators for the neighborhood where each subject lived at the end of the calendar year. The ND score includes the neighborhood's median disposable income, proportion of welfare recipients, proportion of people unemployed, proportion of divorced individuals, proportion of people with only primary school qualifications, proportion of immigrants, residential mobility rate, and criminal conviction rate. The ND scores were transformed to z scores, with higher ND scores corresponding to higher levels of "deprivation" in the subject's neighborhood.

The subject's average Family Income was computed as the arithmetic mean from the annual values of the subject's family's disposable income, as recorded in the Swedish Tax Registry for each year. All yearly income values were adjusted for inflation and scaled to the 2015 Swedish Krona.

Diagnoses of Attention Deficit Hyperactivity Disorder (ADHD) often precede a diagnosis of problematic aggressive behavior, and some researchers view Oppositional Defiant Disorder (ODD) as a lesser form of aggression [14, 17, 37]. ADHD is characterized by a persistent pattern of inattention and hyperactivity, and ODD symptoms, which are typically less severe than the symptoms of CD, include having an angry or irritable mood and losing one's temper on a regular basis [17, 18]. While ADHD is not defined by aggressive behavior, research has consistently shown high levels of comorbidity between the ADHD, ODD, and CD [38]. Thus, we included previous ADHD as a predictor as well as ODD.

Previous ADHD diagnoses were defined as diagnoses having occurred prior to an initial diagnosis as defined previously. Subjects were considered to have a previous ADHD diagnosis if they had at least one inpatient or outpatient medical procedure in Sweden where the recorded reason for the visit was an ICD-9 (314, 314J, 314W, or 314X) or ICD-10 (F90.0–9) code for ADHD or if the subject had received a prescription for the ADHD medication Amfetamine, Dexamfetamine, Methylphenidate, or Atomoxetine [32]. Subjects

were considered to have an ODD diagnosis if they had at least one inpatient or outpatient medical procedure in Sweden with a reported ICD-10 code (F91.3) for ODD.

Distal outcomes

The selected distal life outcomes were attempted suicide, criminal conviction, grade score, and average individual income. Attempted suicide was defined as an emergency inpatient or outpatient hospital visit or death due to intentional self harm (ICD-10: X60–X84) as recorded in the Patient Register and the Cause of Death Register [33]. Likewise, subjects' criminal conviction history was based on the National Crime Registry, which records information on all convictions at the age of 15 (the age of criminal responsibility in Sweden) and older, and was defined as any non-traffic offense violation of the penal code [33]. Grade Score was the subject's average grade in school converted into a *z* score, with higher values corresponding to better grades, as recorded by the National School Registry [31]. Average Individual Income was calculated as the arithmetic mean across all annual values of the subject's individual disposable income after age 18, as reported in the Integrated Database for Labor Market Research [30]. Individual income values were scaled to the 2015 value of the Swedish Krona. In addition, the individual's birth year was regressed out to avoid confounding due to the dependence of income on age.

Exploratory analyses

The main interest in this study was the statistical testing of the impact of the age at initial diagnosis of aggression. Since it is known that Type I error rates are inflated if the selection of variables is done using the same data as the significance testing of effects [39], the data were randomly split into an exploratory set of 2000 cases and controls, and a confirmatory set containing the remaining 9632 cases and controls. The data splitting provided the opportunity to explore and mine a large pool of potentially relevant variables in the exploratory partition of the data without compromising the statistical testing carried out in the confirmatory part of the data. This part of the analysis offers a unique opportunity to leverage the information in the Swedish data bases to explore potentially important predictors and outcomes over and above previously reported variables.

Using the exploratory partition of the data, we evaluated the association between potentially relevant background variables with multiple candidates of outcome variables from the domains of mental health, educational performance, economic success, and criminal activity. The selection of predictors and outcomes was based on (1) consideration of coverage of the four desired outcome domains, (2) potential association between a predictor and at least one outcome as defined by a significant association not controlling for multiple testing, and (3) small intercorrelations (< 0.8) between the selected predictors to avoid instability of results due to multicollinearity. The exploratory analyses are described in the Supplemental Materials.

Main analyses

The planned main analyses consisted of two parts. First, the effect of the selected predictors on the four outcomes was analyzed without the potentially mediating effect of age-at-diagnosis (i.e., in Fig. 1 only path 2 is estimated). This part of the analysis, therefore, provides the baseline parameters. The second part includes age-at-diagnosis in the model, that is, all three paths in Fig. 1 are estimated. The comparison of the two models permits addressing the main question of our study, namely whether age-at-diagnosis mediates the relation between background and outcome variables.

Part 1. We compared children with an aggression diagnosis ("cases") and matched controls. Specifically, we carried out a multivariate multiple regression where four of the covariates (i.e., subjects' mother's achieved maximum education level, her criminal conviction history, the subjects' average Neighborhood Deprivation score and average Family Income) predicted the four distal outcomes. The multiple multivariate regression was carried out separately for boys and girls. This part of the analysis provided insight into which of the background variables might put cases at an increased risk to experience detrimental outcomes compared to controls. The model in which all regression parameters were estimated separately for cases and controls was compared to four more constrained models. In each of the four alternative models, the effects of one of the four outcome variables on the covariates were constrained to be equal for cases and controls while keeping the other three effects unconstrained. To assess significance for individual regression coefficients, we controlled for multiple testing using the spectral decomposition method implemented by Nyholt [40]. This method takes into account intercorrelations between variables and provides the significance level adjusted for multiple testing such that Type I error remains at 0.05. In our case, the adjusted significance level was 0.0057.

Part 2. The second analysis consisted of a two-group (boys and girls) continuous time Cox proportional hazard model using only the case subjects. The aim of part 2 was to investigate whether age at the time of diagnosis mediates the effects on later life outcomes [41] (see Fig. 1) for diagnosed children. All effects were estimated simultaneously. We compared three models. In the first model, all effects were sex specific; in model 2, the effects of age at diagnosis onto the outcomes ("Path 3" in Fig. 1) were constrained to be the same for boys and girls; and in model 3, all effects of time-to-diagnosis on the covariates ("Path 1" in Fig. 1) were
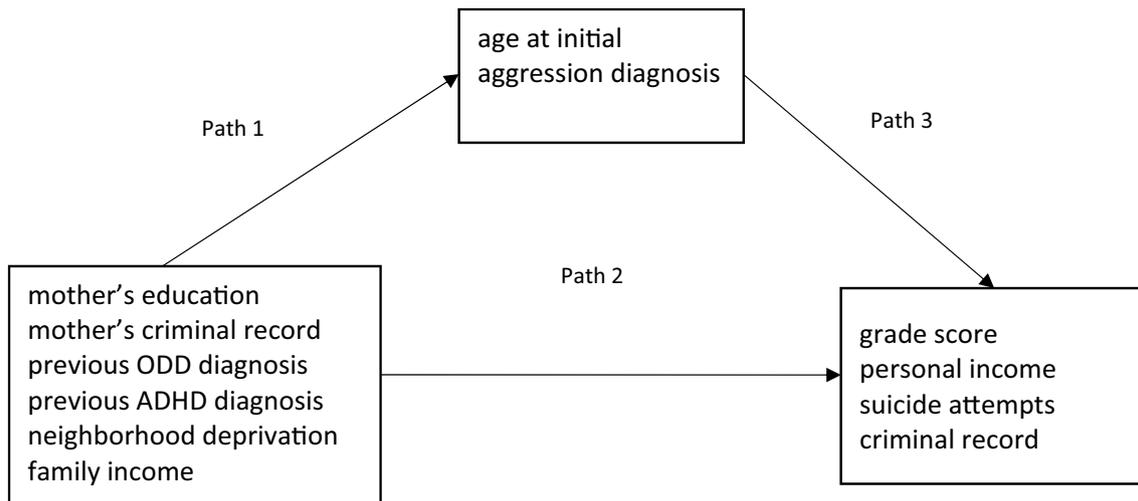
Fig. 1 Time-to-event model. The path diagram above shows the structure of the three time-to-event models in which age at initial aggression diagnosis was modeled as a mediator

also constrained to be sex invariant. In Mplus, we used the mixture setting in combination with the "knownclass" option to carry out the multi-group analysis. This setting permits regressing group membership (i.e., sex of the child) on the covariates such that differences between girls and boys (e.g., ADHD, ODD prevalence) are accounted for. In addition, in all three models, the *direct* effects of the covariates on the outcomes ("Path 2" in Fig. 1) were always allowed to be sex specific.

The models in both parts of our analyses were fitted using Mplus version 7.4 [42]. Likelihood ratio tests were done in *R* [43].

Results

Main analyses

The confirmatory data set contained $N = 4816$ cases (2688 boys and 2128 girls) and an equal number of matched controls. The descriptive statistics for the selected outcomes and covariates for male and female cases and controls are presented in Table 1. The distributions of age at time of initial diagnosis for both male and female cases in the confirmatory set are presented in Fig. 2.

Part 1: Multivariate multiple regression. For boys, the covariate effects on grade score and on suicide attempts could not be constrained to be the same for cases and controls (boys: likelihood ratio test statistic (LRTS) grade score = 11.598, $df = 4$, p value = 0.0206, LRTS suicide = 15.744, $df = 4$, p value = 0.0034). For girls, only the effects on personal income corrected for age could not

be constrained to be equal for cases and controls (LRTS income = 18.386, $df = 4$, p value = 0.001). All effects were, however, always in the same direction for cases and controls.

At the significance level adjusted for multiple testing ($\alpha = 0.0057$, see method section), grade score was positively associated with mothers' education and negatively with neighborhood deprivation for male cases. For male controls, grade score was also associated with mother's criminal record and family income. There was a tendency for suicide attempts to be predicted by worse neighborhood deprivation, but this effect did not reach statistical significance. Suicide attempts were significantly predicted by a lesser family income in the controls, but not in the cases. For both the male cases and controls, having a criminal record was significantly predicted by all four covariates (lower educational level of the mother, mother having a criminal record, higher neighborhood deprivation, and lower family income). Personal income of males was significantly predicted by the educational level of the mother and less severe neighborhood deprivation. In controls, mothers' criminal record and family income were also significantly associated with grade score.

For girls, the personal income for controls was significantly predicted by lower neighborhood deprivation and higher family income. These effects did not reach significance in the case group. Effects that could be constrained to be the same for cases and controls were as follows: Criminal records were predicted by mothers' criminal record and lower family income. Grade score was significantly predicted by all four covariates, and in the same direction as for the boys with detrimental effects of mother having a criminal record and higher neighborhood deprivation, and beneficial effects of higher educational level of the mother and higher

Fig. 2 Distribution of age at time of initial diagnosis for boys and girls. The distribution of ages at time of initial diagnosis for both boys ($N=2688$) and girls (2128) in the confirmatory data set
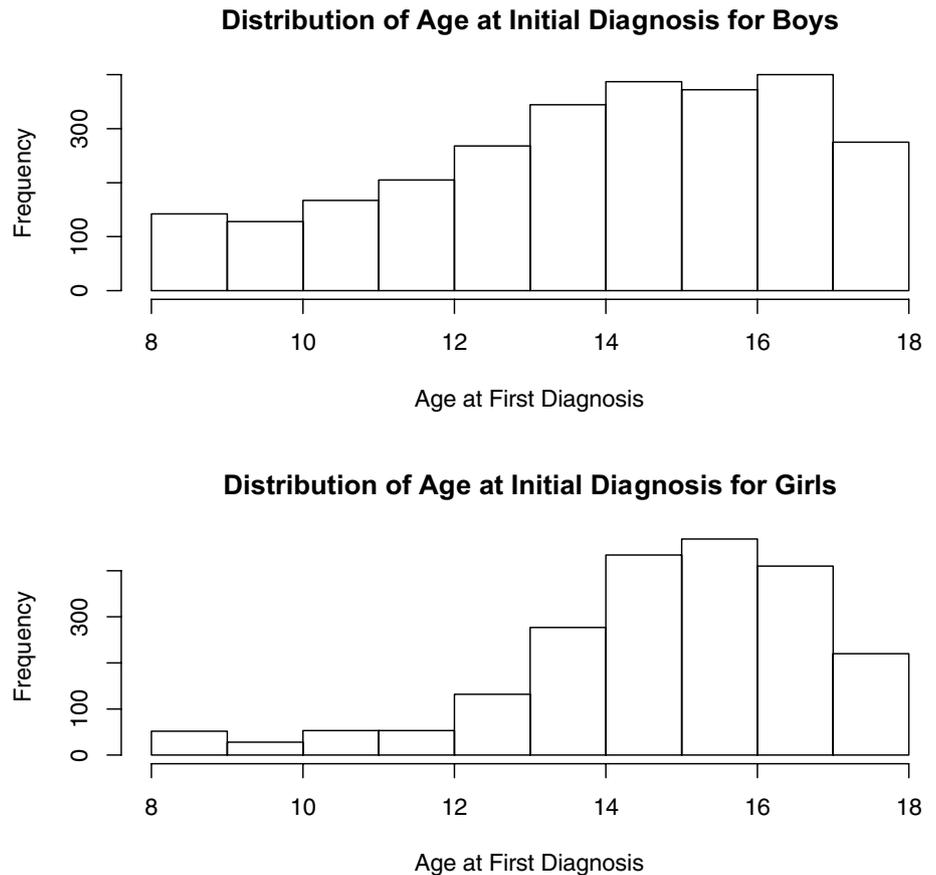

Distribution of Age at Initial Diagnosis for Boys

Distribution of Age at Initial Diagnosis for Girls

Table 1 Descriptive statistics of covariates and distal outcomes for female and male cases and controls

	Female case		Female control		Male case		Male control	
	Mean	SD	Mean	SD	Mean	Sd	Mean	SD
Suicide attempt	0.7%	8.1%	2.0%	13.9%	0.4%	6.7%	0.7%	8.4%
Crime	33.4%	47.2%	7.4%	26.2%	54.6%	49.8%	16%	36.7%
Grade score	−0.745	1.265	0.184	1.054	−0.979	1.233	−0.147	0.929
Personal income	0.146	2.296	−0.133	2.44	−0.121	2.577	0.106	3.124
Mother education	3.724	1.382	4.004	1.422	3.637	1.385	4.08	1.441
Mother crime	25.2%	43.4%	12.8%	33.4%	27.2%	44.5%	13.0%	33.7%
Neighborhood deprivation	0.239	0.82	0.078	0.919	0.281	0.883	0.065	0.938
Family income	3.46	2.611	4.708	2.725	3.662	3.179	5.056	3.277
ADHD	46.2%	49.9%	0	0	61.3%	48.7%	0	0
ODD	13.7%	34.4%	0	0	21.7%	41.2%	0	0

The first four rows are the outcome variables: whether or not the subject has at least one suicide attempt, whether or not the subject has at least one criminal conviction, grade score average as a z score, and personal income adjusted for inflation and measured in millions of SEK (residual value after regressing on age). The last six rows are the covariates: mother's educational level on a 1–7 scale, whether or not the mother has at least one criminal conviction, neighborhood deprivation as a z score, average family income adjusted for inflation and measured in of SEK, and whether or not the subject has a previous ADHD or ODD diagnosis (by definition zero for controls). The mean of the five indicator variables (suicide attempt, crime, mother crime, ADHD, and ODD) is the proportion of the sample with that condition, so these values are presented as percentages. There were 2688 male case subjects and 2128 female case subjects in the confirmatory data set, with an equal number of matched controls

family income. Suicide attempts were not associated with any of the covariates. For more details and estimated effect sizes, see Table 4.

It is interesting to note that several effects were significant in the control group but not in the case group. A set of post hoc mixture analyses described in the Supplemental

Materials support the explanation that the case group is more heterogeneous with respect to the pattern of regression effects, thus reducing overall effect sizes.

Time-to-event analysis. Neither the difference between model 1 (all effects sex specific) and model 2 (regression of outcomes on age of diagnosis not sex specific) was significant (LRTS = 8.012, $df = 4$, p value = 0.091), nor the difference between model 2 and model 3 (age of diagnosis on covariates also not sex specific) (LRTS = 8.386, $df = 6$, p value = 0.211). Taken together, these model comparisons show that the effects were very similar for boys and girls. Note that the effect of regressing suicide attempts on ODD diagnoses was not estimated in these models due to the fact that there were no case subjects with an ODD diagnosis who had a record of attempted suicide.

Table 3 shows the results of the time-to-event analysis on grade score, personal income, criminal record, and suicide attempts. Importantly, the individual's criminal record and average income (corrected for birth year) were significantly predicted by age of diagnosis, over and above any direct effects. A later rather than earlier diagnosis significantly predicted a higher probability of having a criminal record (p value < 0.005), with an odds ratio of 1.126. Note that time-to-event was considered as continuous; hence, the odds ratio is the effect over the total time period (age 8–age 18). Figure 3 shows that this effect appears to be roughly linear, with the probability of having a criminal conviction later in life rising as a child's age at first diagnosis increases across the age range. Table 2 provides the total number and percent of case subjects who had a criminal conviction grouped by age at time of diagnosis. To ensure that only criminal convictions were considered that occurred *after* the first diagnosis, we also fitted the models to data limited to subjects diagnosed before age 15, which is the minimum age of a criminal record in our data. Although the number of cases in this additional analysis decreased to $N = 2563$, the effect on criminal records was still statistically significant, showing an odds ratio of 1.136.

Average income was also significantly predicted by age at time of diagnosis, over and above any direct effects. Personal income was lower as age at initial diagnosis increased, with a regression coefficient of $b = -0.055$, se = 0.015, $t = -3.610$, p value < 0.005. Figure 3 shows that this effect, excluding age 8, is roughly linear with most of the decrease in individual income coming when age at first diagnosis is 16 or higher. Table 2 provides the average individual income for the 4816 case subjects grouped by age at diagnosis. The effect of age at diagnosis onto suicide attempts was not significant after correcting for multiple testing (the observed p value of this effect was 0.016, see Table 3). As Table 2 shows, 25 of the 26 case subjects who had a suicide attempt were 14 or older at the time of their first diagnosis, although this effect was not statistically significant. Grade score was not significantly affected by age at first diagnosis.

Importantly, none of the regressions of age at time of diagnosis on the covariates were significant except for a positive effect on ODD diagnoses. This means that the effects of age at initial diagnosis onto criminal records and personal income are independent of neighborhood deprivation, mother's education and criminal record, and family income.

The pattern of direct effects of the covariates on the four outcomes matched the results of the multivariate multiple regression effects of the cases. Criminal records were positively predicted by mother's criminal record, neighborhood deprivation, and also by previous ADHD diagnoses. Grade scores were predicted by mother's education, neighborhood deprivation, family income, and ADHD diagnosis. Personal income was negatively affected by neighborhood deprivation. The effect of neighborhood deprivation onto suicide attempts did not reach significance.

Discussion

This study was a first attempt to investigate whether the age at first diagnosis of problem behaviors related to aggression has any impact on outcomes during late adolescence or early adulthood. The focus was on school grades, income, criminal records, and suicide attempts. The main finding was that a later diagnosis predicts a higher probability of having a criminal record after age 15 and a lower income as a young adult. Age at time of diagnosis did not affect grade scores. The effect of age at time of diagnosis on suicide attempts was not significant after correcting for multiple testing. Importantly, the analyses showed that the predictive effects of the timing of when the diagnosis occurred on later income and criminal records are independent of effects of background variables that were included in the analyses (i.e., mother's education and criminal records, neighborhood deprivation, family income, ADHD and ODD diagnoses). The effects were very similar for boys and girls.

Our results point in the direction that an early diagnosis could provide the basis for intervention and treatment settings, which may influence the developmental trajectory into later criminality. While very few larger-scale studies have investigated the specific effects of timing of interventions for any neurodevelopmental or disruptive disorder, early intervention has been shown to be effective, especially in children with high initial risk [44]. Our results are also consistent with the finding that early intervention has a positive effect on long-term outcomes related to criminality [45]. The effects are in line with the understanding that neural plasticity in the developing brain makes it particularly susceptible to a broad range of interventions. However, given the fact that our data did not contain information on the start

Fig. 3 Effect of Age at Initial Diagnosis on Outcomes. These plots show *1* the proportion of case subjects in the confirmatory data set with a criminal conviction, *2* the average personal income level, adjusted for inflation and measured in thousands of SEK (residual after regressing out age), *3* the proportion of case subjects with a suicide attempt, and *4* the average grade score (on a *z* scale) all grouped by how old the case subject was at the time of their initial aggression diagnosis. The effect of age at diagnosis on criminal convictions and average personal income are statistically significant. The effect on suicide attempts is not significant after adjusting for multiple testing, and the effect on grade score is not significant
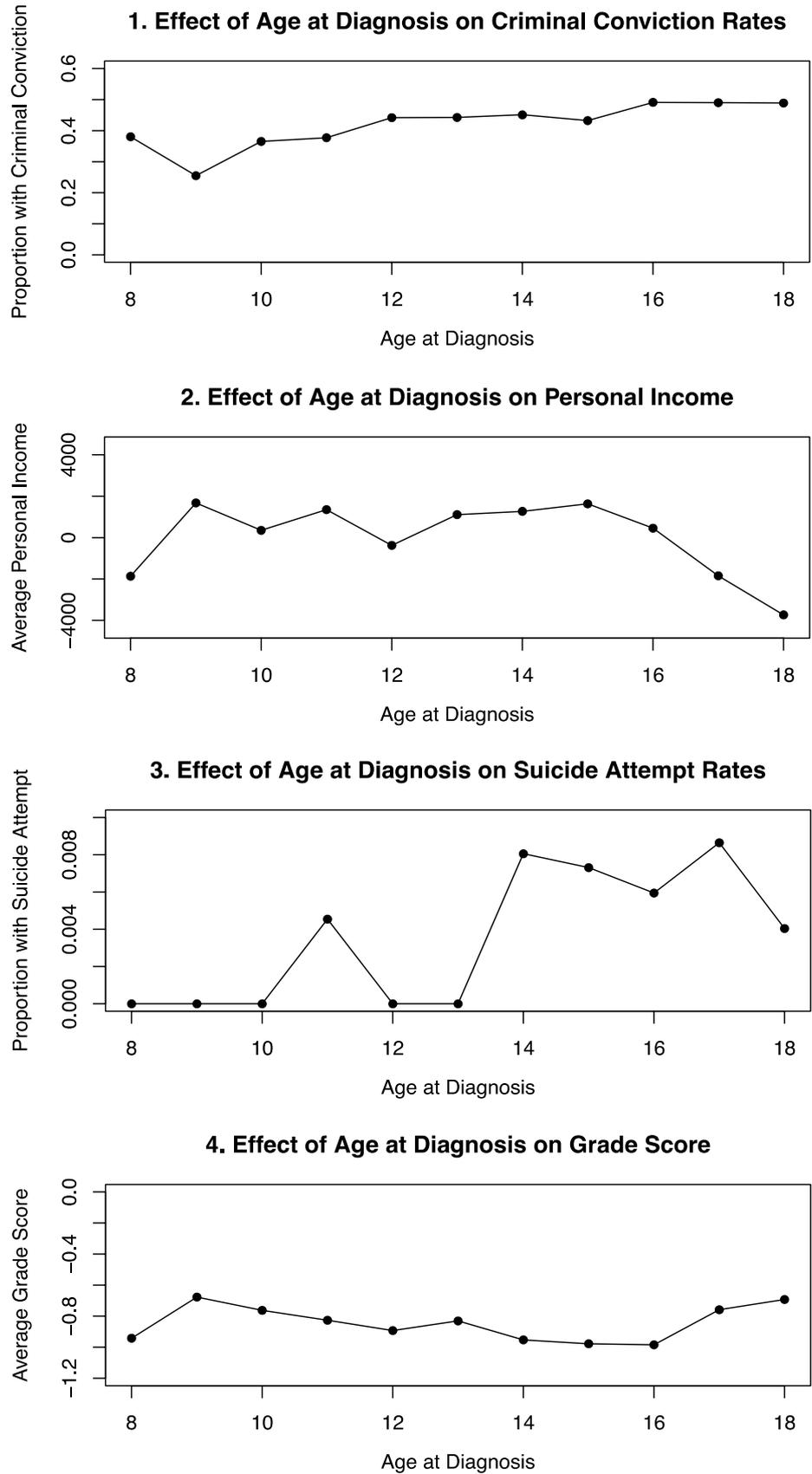
Table 2 Criminal record, suicide attempt, personal income, and grade score grouped by age at diagnosis

Age at diagnosis	N	criminal conviction	Average personal income	Suicide attempt	Average grade score
8	92	35 (38%)	− 1867	0 (0%)	− 0.94
9	102	26 (25%)	1677	0 (0%)	− 0.68
10	156	57 (37%)	352	0 (0%)	− 0.76
11	220	83 (38%)	1352	1 (<0.5%)	− 0.83
12	258	114 (44%)	− 373	0 (0%)	− 0.89
13	400	177 (44%)	1110	0 (0%)	− 0.83
14	621	280 (45%)	1269	5 (1%)	− 0.95
15	821	355 (43%)	1629	6 (1%)	− 0.98
16	841	413 (49%)	456	5 (1%)	− 0.98
17	810	397 (49%)	− 1843	7 (1%)	− 0.76
18	495	242 (49%)	− 3734	2 (<0.5%)	− 0.69
Total/mean	4816	2719 (45%)	3	26 (1%)	− 0.85

Criminal Conviction is the number of case subjects in each group of age of initial diagnosis who have at least one criminal conviction. Average Personal Income is the residual value after regressing age out of average individual income, adjusted for inflation and measured in thousands of SEK. Suicide Attempt is the number of case subjects with at least one suicide attempt. Average Grade Score is the student's average grade in school, measured as a z score. In the last row total values are presented for N, Criminal Conviction, and Suicide Attempt, and mean values are presented for Average Personal Income and Average Grade Score

Table 3 Time-to-event (age at initial diagnosis) on grade score, personal income, criminal record, and suicide attempt

	Time-to-event Age at diagnosis	Four outcomes			
		Grade score	Personal income	Crime	Suicide attempt
Boys					
Previous ADHD	0.052 (0.033)	**− 0.264 (<0.0005)**	− 0.283 (0.013)	**0.657 (<0.0005)**	− 0.319 (0.573)
ODD	**0.306 (<0.0005)**	0.035 (0.777)	0.035 (0.777)	− 0.080 (0.444)	Not estimated
Mother education	− 0.010 (0.261)	**0.107 (<0.0005)**	− 0.094 (0.013)	− 0.083 (0.010)	0.083 (0.769)
Mother crime	0.026 (0.355)	0.019 (0.751)	− 0.072 (0.518)	**0.459 (<0.0005)**	− 1.311 (0.190)
Neighborhood deprivation	0.025 (0.098)	**− 0.102 (<0.0005)**	**− 0.266 (<0.0005)**	**0.173 (0.001)**	− 0.853 (0.071)
Family income	0.006 (0.168)	**0.034 (0.005)**	0.053 (0.041)	− 0.083 (0.011)	− 0.037 (0.573)
Girls					
Previous ADHD	Constrained to be the same for boys and girls	**− 0.416 (<0.0005)**	**− 0.307 (0.002)**	**0.725 (<0.0005)**	− 0.236 (0.720)
ODD		0.016 (0.847)	0.193 (0.208)	− 0.162 (0.272)	Not estimated
Mother education		**0.153 (<0.0005)**	0.006 (0.871)	− 0.003 (0.932)	− 0.197 (0.458)
Mother crime		**− 0.211 (0.003)**	0.075 (0.533)	**0.480 (<0.0005)**	− 1.231 (0.237)
Neighborhood deprivation		− 0.067 (0.071)	− 0.126 (0.030)	0.105 (0.080)	− 0.287 (0.272)
Family income		**0.055 (<0.0005)**	− 0.033 (0.092)	**− 0.165 (<0.0005)**	− 0.061 (0.544)
Constrained to be the same for boys and girls					
Age at diagnosis	–	− 0.005 (0.505)	**− 0.055 (<0.0005)**	**0.119 (<0.0005)**	0.234 (0.016)

Regression coefficients and p values (within brackets) of Model 3. The significance level corrected for multiple testing is 0.0057, and significant effects are presented in bold. Model 3 is the survival model in which only the direct effects ("Path 2" in Fig. 1) are permitted to be sex specific (see methods section). The effects of the predictors on the age of diagnosis ("Path 1" in Fig. 1) are constrained to be the same for boys and girls, as is the effect of age at diagnosis on the 4 outcomes ("Path 3" in Fig. 1). Note that effects of suicide attempts on ODD diagnosis were not estimated because none of the ODD cases had recorded suicide attempts (see "Method" section)

of any treatment, some caution is warranted. For instance, it could also be possible that a later diagnosis is merely indicative of persistence, which in turn might be related to poorer outcomes.

In addition to the main analyses focusing on age at time of initial diagnosis, we also compared cases and controls in a multivariate multiple regression to assess the predictive effects of mother's education and criminal history,

neighborhood deprivation and average family income on suicide attempts, criminal records, grades, and income without taking into account age at diagnosis. All four outcomes were associated with one or more of the predictor variables in both boys and girls (see Table 4 for details). These effects were very similar to the covariate effects found in the time-to-event analysis, in accordance with the finding that the effects of the age at diagnosis are independent of these covariate effects. Interestingly, multiple effects were more pronounced in controls compared to cases. A possible explanation is that cases are more heterogeneous with respect to the pattern of regression effects of the background variables onto the four outcomes, leading to non-significant results overall. In secondary analyses, we fitted the multiple multivariate regression models as mixture models with additional classes. The results showed that based on BIC, more classes improved the fit for cases, but not for controls. This finding provides an interesting angle for future research as it indicates that subgroups of cases with a higher risk of

detrimental outcomes characterized by specific patterns of background variables may be identifiable.

Limitations

The current study has several limitations. As other studies that utilize registry data have indicated [30–33, 46], there are certain benefits and limitations to analyzing registry data. The larger sample size they provide comes at the cost of limited flexibility with how the data are collected and how variables are operationalized. For instance, we did not have data indicating the severity of the initial aggression diagnosis nor the different symptom combinations that led to the given diagnosis. On the other hand, the Swedish Data Registries have been validated for several conditions. Idring et al. [47] scrutinized medical records in several registers, and reported a high correlation between medical records and registered diagnoses of ASD. Validation studies have also been conducted for tic disorder, obsessive compulsive

Table 4 Multivariate multiple regression of distal outcomes on covariates

	Grade score		Personal income		Crime		Suicide attempt	
	Effect size (SE)	*p* value	Effect size (SE)	*p* value	Effect size (SE)	*p* value	Effect size (SE)	*p* value
Boys								
Mother education	**0.113 (0.021)/0.157 (0.014)**	**0.000/0.000**	− 0.101 (0.030)	**0.001**	− 0.089 (0.025)	**0.000**	0.100 (0.290)/− 0.087 (0.180)	0.729/0.631
Mother crime	0.007 (0.059)/**− 0.201 (0.054)**	0.901/**0.000**	0.173 (0.101)	0.086	**0.527 (0.079)**	**0.000**	− 1.321 (0.999)/0.831 (0.499)	0.186/0.096
Neighborhood deprivation	**− 0.100 (0.036)/− 0.086 (0.028)**	**0.005/0.002**	− 0.341 (0.045)	**0.000**	**0.211 (0.041)**	**0.000**	− 0.881 (0.498)/− 0.373 (0.214)	0.077/0.081
Family income	0.034 (0.013)/**0.029 (0.006)**	0.006/**0.000**	**0.050 (0.018)**	**0.005**	− 0.087 (0.024)	**0.000**	− 0.041 (0.120)/**− 0.504 (0.153)**	0.732/**0.001**
Girls								
Mother education	**0.174 (0.014)**	**0.000**	0.008 (0.039)/− 0.088 (0.040)	0.834/0.025	− 0.015 (0.033)	0.654	− 0.029 (0.114)	0.798
Mother crime	**− 0.212 (0.050)**	**0.000**	0.069 (0.122)/0.084 (0.163)	0.571/0.604	**0.565 (0.097)**	**0.000**	0.378 (0.358)	0.290
Neighborhood deprivation	**− 0.081 (0.023)**	**0.000**	− 0.112 (0.059)/**− 0.226 (0.063)**	0.056/**0.000**	0.110 (0.051)	0.030	0.028 (0.158)	0.859
Family income	**0.061 (0.009)**	**0.000**	− 0.029 (0.020)/**0.080 (0.023)**	0.150/**0.001**	− 0.160 (0.029)	**0.000**	− 0.136 (0.078)	0.083

The rows are mother's educational level on a 1–7 scale, whether or not the mother has at least one criminal conviction, neighborhood deprivation as a *z* score, and average family income adjusted for inflation and measured in thousands of SEK. The columns are the four outcome variables: grade score average as a *z* score, personal income adjusted for inflation and measured in thousands of SEK (residual value after regressing on age), whether or not the subject has at least one criminal conviction, and whether or not the subject has at least one suicide attempt. If cases and controls differ with respect to the regression effects two *p* values are shown (cases first). The significance value corrected for multiple testing is 0.0057. Significant effects at this level are shown in bold

disorders, and psychotic disorders, and high reliability and validity have been reported for these conditions [48, 49].

As Chang et al. [30] point out, registry studies are inherently observational in nature, so causal interpretations are inappropriate due to the possible influence of other variables. For example, childhood aggression is known to co-occur with substance abuse issues, which can also lead to detrimental outcomes such as those seen in this study [6, 13, 50]. It is possible that substance abuse contributes both to greater aggression and to the negative outcomes in this study, or that either aggression or substance use mediates the effect of the other on outcome variables. With observational data such as are available in data registries, causal implications are unclear and the influence of other factors is impossible to rule out.

We acknowledge the low prevalence of diagnosed problematic aggressive behavior, possibly due to a reluctance of clinicians to assign a diagnosis in the presence of another previously diagnosed disorder (e.g., ADHD). The low prevalence of diagnoses can be deducted from data showing that Sweden's population in 2013 was estimated to be 9.6 million people [51], while 17,044 people recorded with an initial diagnosis in the Swedish data registries. The 5816 case subjects in this study were born between 1987 and 1995, during which time just over 1 million live births were recorded in Sweden [51]. Furthermore, the lack of data regarding the type and length of treatment also precludes a definite conclusion about the importance of age at diagnosis. However, as an initial investigation into the effects of the age at diagnosis on later in life outcomes, the general trend of earlier diagnoses resulting in better outcomes merits further investigations into the effectiveness and impact of different treatment options available at the time of the aggression diagnosis.

The benefit of registry studies is large-scale, systematic data collection that does not place any additional data collection burdens on the subjects. Children's medical visits in Sweden were already being recorded by the medical professionals, so children who had aggression problems could be included in this study without the need for them or their families to fill out an additional survey or respond to data collection requests. Similarly, the tax and school records were already collected by the Swedish government, so these variables could be analyzed without the need to question individuals directly. Additionally, all the variables in the analysis were collected and defined the same way for every subject, allowing for a systematic investigation into effects of interest.

Finally, all data used in this study were collected in Sweden, thus, limiting the generalizability of results to other countries where diagnosis of aggression, treatment, and the pattern of factors influencing outcomes such as those used in the current study might be different. For example, Broidy et al. [5] found differences in the developmental trajectories of childhood aggressive behavior across Canada, the United States, and New Zealand. In the future, we plan to utilize data from the ACTION consortium to assess similarity of results across different European countries [52, 53]. Also, even with large samples such as the one used in this study, associations with suicide attempts are challenging to estimate due to the low prevalence. Although the effect of the timing of initial diagnosis was not statistically significant in our study after correcting for multiple testing, any factor that may reduce the risk of suicide attempts in adolescents clearly deserves additional research.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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