# Early-Life Injuries and the Development of Attention-Deficit/Hyperactivity Disorder

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## ABSTRACT

***Objective:*** To estimate phenotypic and familial association between early-life injuries and attention-deficit/hyperactivity disorder (ADHD) and the genetic contribution to the association using polygenic risk score for ADHD (PRS-ADHD) and genetic correlation analyses.

***Methods:*** Children born in Denmark between 1995–2010 (n = 786,543) were followed from age 5 years until a median age of 14 years (interquartile range: 10–18 years). Using *ICD-10* diagnoses, we estimated hazard ratios (HRs) and absolute risks of ADHD by number of hospital/emergency ward–treated injuries by age 5. In a subset of ADHD cases and controls born 1995 to 2005 who had genetic data available (n = 16,580), we estimated incidence rate ratios (IRRs) for the association between PRS-ADHD and number of injuries before age 5 and the genetic correlation between ADHD and any injury before age 5.

***Results:*** Injuries were associated with ADHD (HR = 1.61; 95% CI, 1.55–1.66) in males (HR = 1.59; 1.53–1.65) and females (HR = 1.65; 1.54–1.77), with a dose-response relationship with number of injuries. The absolute ADHD risk by age 15 was 8.4% (3+ injuries) vs 3.1% (no injuries). ADHD was also associated with injuries in relatives, with a stronger association in first- than second-degree relatives. PRS-ADHD was marginally associated with the number of injuries in the general population (IRR = 1.06; 1.00–1.14), with a genetic correlation of 0.53 (0.21–0.85).

***Conclusions:*** Early-life injuries in individuals and their relatives were associated with a diagnosis of ADHD. However, even in children with the most injuries, more than 90% were not diagnosed with ADHD by age 15. Despite a low positive predictive value and that the impact of unmeasured factors such as parental behavior remains unclear, results indicate that the association is partly explained by genetics, suggesting that early-life injuries may represent or herald early behavioral manifestations of ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is more difficult to validly diagnose before 5 years of age, as the diagnostic criteria relate mainly to older children, and the clinical presentation of ADHD may differ in preschool and school. Besides subthreshold symptoms of inattention, hyperactivity, and impulsivity, little is known about early-life manifestations of ADHD.[1] In typically developing children, impulsive and risk-taking behavior is more common at a younger age,[2] as are injuries.[3,4] The ability to plan ahead and foresee unsafe situations improves with age, as executive brain functions mature,[5] and this cognitive maturation is paralleled by a decrease in the risk of injuries.[6] Since the 1960s, studies of preschool children have found injuries to be correlated with inattention, hyperactivity, and impulsivity.[7–11] Meta-analyses provide strong evidence that individuals with ADHD have increased risk of emergency ward visits[12] and unintentional injuries.[13–15] Traumatic brain injury (TBI) may be causally linked to ADHD,[16–18] whereas literature on whether other injuries early in life tend to precede a diagnosis of ADHD is sparse.

ADHD is a neurodevelopmental disorder,[19] with heritability estimates of around 74%.[20] Independently derived ADHD polygenic risk score (ADHD-PRS) predicts ADHD status,[21] subthreshold ADHD symptoms,[22] and other neurodevelopmental traits in the general population.[23] Genome-wide association studies (GWAS) recently identified several genome-wide significant loci and estimated that common genetic variants explain 22% of the heritability of ADHD.[24]

Less is known about the etiology of early-life injuries. Recently, a Danish register-based study found maternal depression to be associated with injuries during early childhood,[25] and depression and ADHD are genetically correlated.[24] A twin study suggested a small genetic contribution to injuries before age 5, with most variance

**Clinical Points**

- Attention-deficit/hyperactivity disorder (ADHD) is associated with increased injury risk. Yet, it is unknown whether early-life injuries are early manifestations of ADHD and possibly linked to ADHD genetics in the general population.
- In clinical assessments of schoolchildren suspected of having ADHD, information on number of sustained injuries before age 5 may further support the diagnosis of ADHD, as these behaviors are genetically linked to one another.

explained by child-specific environmental effects (including ADHD symptoms) and familial effects, several of which are known risk factors for ADHD, such as low socioeconomic status (SES) and young and single parenthood.[26] Similarly, a Finnish twin study found little indication of a genetic contribution to injuries in adults.[27] However, Acar et al[28] found that fathers of children admitted to the emergency ward due to an injury had higher ADHD symptom scores themselves compared with fathers of children acutely admitted to hospital due to a throat infection. The cross-generational association between ADHD and injuries may be explained by home environment, parental behavior, parent-child interactions, or genetics.

We hypothesize that, similarly to early subthreshold symptoms of ADHD, injuries before age 5 may be early manifestations of ADHD and may associate with ADHD genetic liability. Using a large Danish population-based cohort, our aims were to (1) estimate the association between the number of injuries before age 5 and a later diagnosis of ADHD, (2) estimate the association between early-life injuries in siblings and parents and the risk of ADHD, and (3) estimate the association between ADHD-PRS and the number of early-life injuries in the general population as well as the genetic correlations between ADHD and early-life injuries.

## METHODS

### Data Sources

Since 1968, the Danish Civil Registration System[29] has held data on personal identification number, sex, date of birth, and continuously updated vital status of all persons living in Denmark, enabling accurate linkage of individual-level data across registers. The Danish National Patient Register (DNPR) and the Danish Psychiatric Central Research Register (DPCRR) hold data on all inpatient admissions and outpatient and emergency ward visits from 1995 onward and provided data on injuries and psychiatric disorders diagnosed in hospital departments.[30,31] Diagnoses were registered according to the *International Classification of Diseases*, 8th revision (*ICD*-8) in 1969–1993 and 10th revision (*ICD-10*)[32] since 1994. The Danish Neonatal Screening Biobank provided dried blood spots, and the Integrative Psychiatric Research (iPSYCH) consortium processed these for genotyping.[33]

### Study Population

This was a population-based cohort study of individuals born in Denmark of Danish-born parents between January 1, 1995, and December 31, 2010, and living in Denmark at age 5. Individuals were excluded if they fulfilled any of these criteria before age 5: ADHD diagnosis or filled prescriptions of ADHD medication, TBI, or disease of the nervous system. Genetic analyses relied on the population-based iPSYCH2012 case-cohort, including all ADHD cases (N = 18,726) and 2% random sample of the general population (subcohort) (N = 30,000).[33] DNA collection, genotyping, and quality control have been described elsewhere.[33] Included individuals (n = 16,580) fulfilled these criteria: singletons; born between January 1, 1995, and December 31, 2005; alive and residing in Denmark at age 1; both parents born in Denmark; and no diagnosis of TBI before age 5. We further restricted to individuals of European ancestry[34] and for genetic correlation analyses to unrelated individuals.[35] See Supplementary Tables 1 and 2 for codes and flow of exclusions of participants.

### Early-Life Injuries

We defined early-life injury in cohort members and their siblings as a hospital-treated injury before age 5. This age cutoff ensured complete coverage of injuries and that injuries preceded the ADHD diagnosis. We included diagnoses of injuries from all hospital contacts (inpatient, outpatient, and emergency ward visits), excluding TBIs (Supplementary Table 1) and contacts due to self-harm (*ICD-10*: X60–X84, or contact reason = 4). These unintentional injuries, not including TBIs, are henceforth termed *injuries*. Injuries were defined as any (yes/no) and as number of injuries (0, 1, 2, 3+). For number of injuries before age 5, consecutive injury contacts within 60 days were considered as 1 injury. An overview of injuries and their sex distribution are shown in Supplementary Table 1.

### Injuries in Relatives

Parental injuries were based on *ICD-8*/*-10* codes (Supplementary Table 1) and defined as at least 2 inpatient admissions due to injuries before 20 years of age, as data on outpatient contacts and emergency ward visits were available only from 1995 onward. For sibling exposures, the study population was restricted to children having at least 1 full/half-sibling fulfilling the same inclusion criteria as the index child, and the exposure measure was 1 if any sibling had an injury before age 5, and 0 otherwise. Additionally, for full siblings, the average number of injuries before age 5 was calculated and classified into 4 categories in line with previous research[36]: no injuries, ]0–1] (interval not including 0 and including 1), ]1–2], and > 2 injuries.

### Diagnoses of ADHD

Using data from DPCRR and DNPR, we defined ADHD as the first hospital contact to a psychiatric, pediatric, or neurologic department with a diagnosis of ADHD (*ICD-10* codes F90.x, F98.8) after the age of 5. ADHD subtypes

**Table 1. Rates and Hazard Ratios of ADHD, Comparing Individuals With No vs Any Injuries and vs Number of Injuries Before Age 5[a]**

| | N | Person-years | N (ADHD) | HR (95% CI) |
|---|---|---|---|---|
| All | 786,543 | 6,910,193 | 23,107 | |
| No injuries | 693,852 | 6,120,395 | 18,850 | 1 |
| ≥ 1 injury[b] | 92,691 | 789,798 | 4,257 | 1.61 (1.55–1.66) |
| 0 | 693,852 | 6,120,395 | 18,850 | 1 |
| 1 | 67,077 | 572,698 | 2,769 | 1.45 (1.40–1.51) |
| 2 | 19,014 | 160,862 | 1,007 | 1.83 (1.72–1.95) |
| 3+ | 6,600 | 56,239 | 481 | 2.48 (2.27–2.72) |
| Males | 401,758 | 3,495,504 | 16,191 | |
| No injuries | 345,125 | 3,019,195 | 12,921 | 1 |
| ≥ 1 injury | 56,660 | 476,309 | 3,270 | 1.59 (1.53–1.65) |
| 0 | 345,125 | 3,019,195 | 12,921 | 1 |
| 1 | 39,936 | 336,618 | 2,108 | 1.45 (1.38–1.52) |
| 2 | 12,219 | 101,929 | 770 | 1.75 (1.63–1.88) |
| 3+ | 4,505 | 37,761 | 392 | 2.46 (2.22–2.72) |
| Females | 384,758 | 3,414,689 | 6,916 | |
| No injuries | 348,727 | 3,101,200 | 5,929 | 1 |
| ≥ 1 injury | 36,031 | 313,489 | 987 | 1.65 (1.54–1.77) |
| 0 | 348,727 | 3,101,200 | 5,929 | 1 |
| 1 | 27,141 | 236,080 | 661 | 1.46 (1.35–1.59) |
| 2 | 6,795 | 58,932 | 237 | 2.12 (1.86–2.41) |
| 3+ | 2,095 | 18,477 | 89 | 2.56 (2.07–3.16) |

[a]The proportional hazards assumption was checked by visual inspection of log-minus-log plots for the exposure variable (injuries [yes/no] and 0, 1, 2, 3+ injuries) and adjustment variables (birth cohort and sex). HRs were adjusted for sex and birth cohort and the interaction between sex and birth cohort. Robust variance estimation was applied to account for siblings.

[b]Among all individuals (with or without ADHD) with an injury before age 5, less than 1% of these had their first injury within the first year of life.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, HR = hazard ratio.

included combined (F90.0) and inattentive (F98.8) subtypes. Based on funding available at the time, sampling of ADHD cases for the iPSYCH2012 case-cohort sample included only cases with *ICD-10* code F90.0.

### Polygenic Risk Scores for ADHD

PRS were derived using both LDpred[37] and BOLT-LMM[38] software and combined in a linear combination to obtain final PRS (see Supplementary Appendix 1).[39] PRS-ADHD was standardized based on the mean and standard deviation in the iPSYCH subcohort, representing the distribution in the general population.

### Statistical Analyses

First, hazard ratios (HRs) were estimated by Cox regression for the association between early-life injuries and ADHD, using age as the underlying time axis. Analyses were repeated for the 2 ADHD subtypes and in strata of parental education (completed high school yes/no). Individuals were followed from their fifth birthday until first ADHD diagnosis, TBI, emigration, or death, whichever came first. Absolute risks were calculated as cumulative incidences of ADHD at ages 10 and 15 years.

Second, we investigated familial coaggregation of injuries and ADHD, estimating HRs for associations between injuries in mothers, fathers, full siblings, maternal and paternal half-siblings (exposures), and ADHD in the index child (outcome). All analyses were adjusted for sex, birth cohort (1995–1998, 1999–2002, 2003–2006, 2007–2010), and the interaction between sex and birth cohort. Analyses of parental injuries were additionally adjusted for the parent's birth cohort (< 1968, 1968–1971, 1972–1977, >1977). Analyses of average number of injuries in siblings were additionally adjusted for the number of full/maternal half/paternal half-siblings (1, 2, 3+).

Third, incidence rate ratios (IRRs) were estimated by negative binomial regression with the logarithm transformed time at risk as an offset for associations between PRS-ADHD and the number of injuries before age 5. Due to the iPSYCH2012 case-cohort sampling design, including all ADHD cases and a 2% random subcohort, inverse sampling probabilities were applied as weights.[40] IRRs correspond to a relative increase in the rate of early-life injuries for an increase of 1 standard deviation in the PRS-ADHD. These analyses were adjusted for sex, age, and calendar year at first ADHD diagnosis (both continuous), genotyping wave (categorical), and the first 4 principal components (PCs) to adjust for potential remaining population stratification. The PCA method for deriving the PCs used for ancestry outlier removal and adjustment is described in detail elsewhere.[34] Follow-up started at birth and ended at age 5, a diagnosis of disease of the nervous system (*ICD-10* codes G00–G99), death, or emigration from Denmark, whichever came first.

All analyses were repeated in males and females and applied a cluster-robust variance estimator with clusters defined as individuals having the same mother and father and for half-sibling cohorts defined as individuals having the same mother or father.

Finally, SNP heritability ($h^2_{SNP}$) and genetic correlation ($r_g$) between early-life injuries and ADHD were estimated using BOLT-REML software among the iPSYCH2012 ADHD cases and subcohort. SNPs were filtered and linkage disequilibrium (LD) pruned according to BOLT-REML suggested guidelines[35] (for details, see Supplementary Appendix 2). Heritability estimates were transformed to the liability scale as proposed by Lee et al,[41] assuming population prevalence of 5% for ADHD and 10% for injuries.

The main analyses were conducted using Stata 15.[42] Plots of cumulative incidences were estimated and plotted using R 3.6.1.[43] All estimates are accompanied by 95% confidence intervals (CIs).

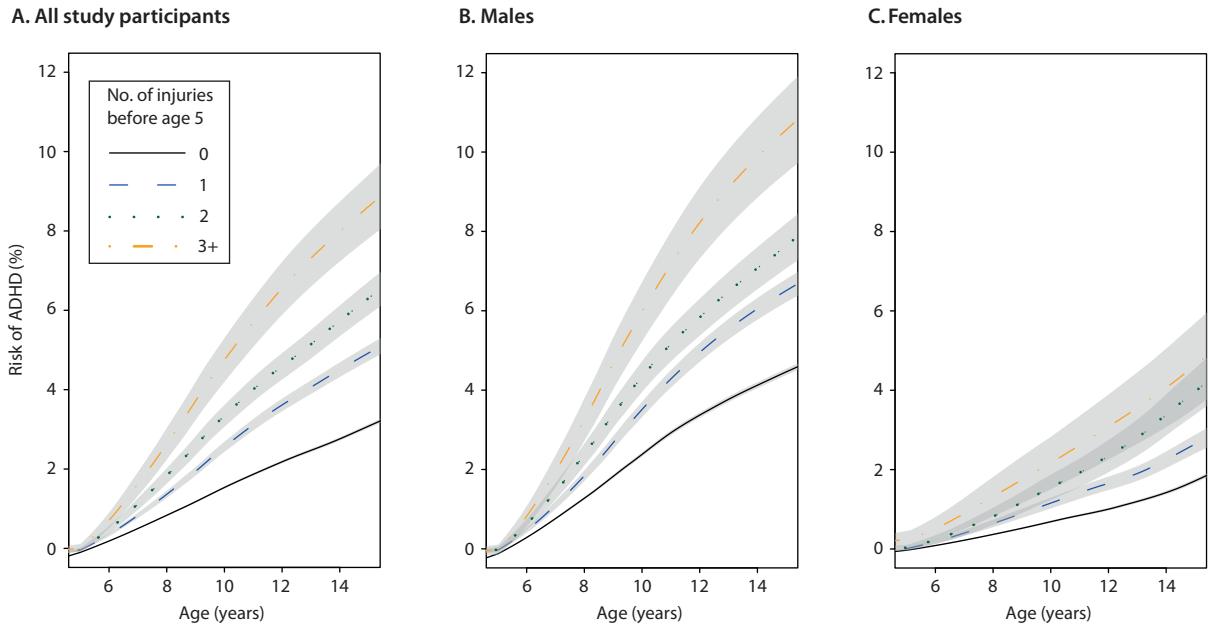
### Ethics

iPSYCH is approved by the Danish Data Protection Agency, the Danish Health Data Authority, the Danish Scientific Ethics Committee, and the Danish Neonatal Screening Biobank Steering Committee.[33,44,45]

## RESULTS

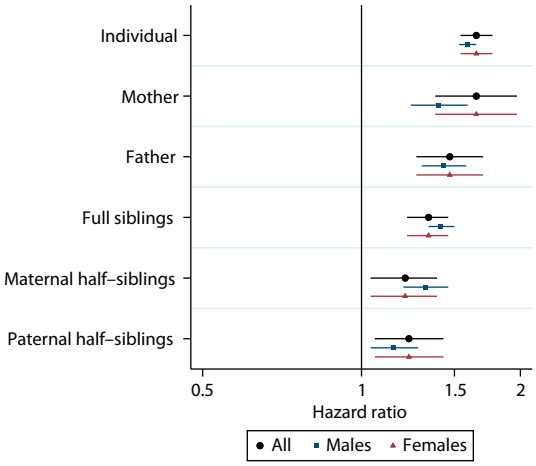
The study population consisted of 786,543 children born in Denmark between 1995 and 2010, followed for a total of 6,910,193 person-years, until a median age of 13.9 years (interquartile range: 9.9–18.0). In total, 92,691 individuals

**Figure 1. Cumulative Incidence Functions for ADHD After Age 5 by Number of Injuries Before Age 5[a]**




[a]Cumulative incidences of ADHD after age 5 with 95% confidence interval (y-axis) by age (x-axis), estimated for different exposure groups (≥3, 2, 1 and 0 injuries before age 5).
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

**Figure 2. Associations Between Injuries and ADHD[a]**




[a]Individual and familial associations between injuries and ADHD in the index individual. The exposure was defined as at least 1 injury before age 5 for individual and siblings and at least 2 inpatient admissions due to injuries before age 20 in parents. All analyses were adjusted for sex, birth cohort, and the interaction between sex and birth cohort. Sibling exposure and analyses were additionally adjusted for number of siblings. Parental exposure analyses were additionally adjusted for parent's birth cohort.
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

(11.8%) sustained an injury before age 5, and 23,107 individuals (2.9%) were diagnosed with ADHD after 5 years of age and during follow-up. In 34,452 study participants (4.4%), follow-up ended due to death (n = 423), emigration from Denmark (n = 11,704), or TBI (including concussion) after age 5 (n = 22,053).

### Association Between Injuries and ADHD

Having sustained at least 1 injury before age 5 was associated with a subsequent diagnosis of ADHD (HR = 1.61; 95% CI, 1.55–1.66). Furthermore, an increasing number of injuries was associated with an increased risk of ADHD, suggesting a dose-response relationship (Table 1). Children with 3 or more injuries had a 2.5-fold increased risk of ADHD (HR = 2.48; 95% CI, 2.27–2.72) when compared to children with no injuries.

We found no significant interaction between injuries (yes/no) and sex ($P = .455$), and associations were similar in sex-specific analyses (Table 1).

We observed a dose-response relation with higher cumulative incidence of ADHD by increasing number of injuries before age 5 (Figure 1 and Supplementary Table 3). By 15 years of age, the estimated risk of ADHD ranged from 3.05% (95% CI, 3.00%–3.10%) in children with no injuries to 8.43% (95% CI, 7.64%–9.22%) in children with 3 or more injuries. Similar patterns were seen in both sexes (higher absolute risks in males), for ADHD subtypes (strongest associations for the combined subtype), and across strata of parental education (Supplementary Tables 4 and 5).

### Familial Coaggregation of Injuries and ADHD

ADHD was associated with injuries in first-degree relatives, including mothers (HR = 1.47; 1.32–1.64), fathers (HR = 1.45; 1.33–1.57), and full siblings (HR = 1.39; 1.33–1.46) (Figure 2 and Supplementary Table 6). The association was somewhat weaker in second-degree relatives, including maternal half-siblings (HR = 1.28; 1.18–1.40) and paternal half-siblings (HR = 1.18; 1.08–1.29). The number of injuries

**Table 2. Association Between PRS-ADHD and Number of Injuries Before 5 Years of Age in iPSYCH ADHD Cases and Subcohort (16,580) and in Males (n = 10,430) and Females (n = 6,150) Separately**

| Exposure Cohort | Cases, N | Person-years | Total no. of injuries before age 5 | Rates[a] of injuries per 100 person-years | IRR[b,c] for injuries (95% CI) |
|---|---|---|---|---|---|
| PRS—All | 16,580 | 81,521 | 3,637 | 4.46 (4.32–4.61) | 1.06 (1.00–1.14) |
| PRS—Males | 10,430 | 51,258 | 2,686 | 5.24 (5.04–5.44) | 1.04 (0.96–1.13) |
| PRS—Females | 6,150 | 30,264 | 951 | 3.14 (2.95–3.35) | 1.09 (0.98–1.22) |

[a]Rates are here presented unadjusted and unweighted.
[b]Analyses were adjusted for sex, genotyping wave, the first 4 principal components to correct for population stratification, and birth cohort. Cluster-robust variance estimation was applied to account for clustering by siblings.
[c]Adjusted and weighted IRR were estimated from a negative binomial regression analysis and weighted to represent associations in the general population.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, iPSYCH = The Lundbeck Foundation Initiative for Integrative Psychiatric Research, IRR = incidence rate ratio, PRS = polygenic risk score.

**Table 3. SNP-Based Heritability Estimates of ADHD and Early-Life Injuries and Genetic Correlation Calculated[a] in iPSYCH ADHD Cases and Subcohort (n = 14,333)**

| Phenotype | Cases, N (%) | SNP-based heritability $h^2_{SNP}$ (95% CI) | Liability scale heritability[b] $h^2_{Liab}$ (95% CI) | Genetic correlation $r_g$ (95% CI) |
|---|---|---|---|---|
| ADHD | 6,186 (43.2) | 0.33 (0.28–0.39) | 0.28 (0.24–0.33) | 0.53 (0.21–0.85) |
| Any injury before age 5 | 2,137 (14.9) | 0.06 (0.01–0.11) | 0.13 (0.02–0.23) | |

[a]BOLT-REML estimation on an LD-pruned set of SNPs (n = 785,388).
[b]Heritability estimates were transformed to the liability scale assuming population prevalence of 5% for ADHD and 10% for injuries. Sample prevalences were higher (43% and 16%, respectively) mainly due to oversampling of ADHD cases in the iPSYCH sample.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, $h^2_{liab}$ = liability scale heritability, $h^2_{SNP}$ = SNP-based heritability, iPSYCH = The Lundbeck Foundation Initiative for Integrative Psychiatric Research, LD = linkage disequilibrium, REML = restricted maximum likelihood, $r_g$ = genetic correlation, SNP = single-nucleotide polymorphism.

in full siblings also increased the HR of ADHD in the index child incrementally. An average number of >2 injuries in full siblings was associated with an increased risk of ADHD (HR = 1.81; 1.54–2.14) when compared to the risk of ADHD in full siblings without injuries. Similar sex-specific trends were observed (Supplementary Table 6).

### Genetics of ADHD and Injuries

In a subset of the general population with genetic data available (n = 16,580), a higher PRS-ADHD was associated with a higher number of injuries before age 5 (IRR = 1.06; 1.00–1.14), with similar-sized estimates for males and females (Table 2). In unrelated individuals (n = 14,333), we found moderate SNP-based heritability for ADHD and low SNP-based heritability for early-life injuries, with strong evidence for genetic correlation between the two ($r_g$ = 0.53; 95% CI, 0.21–0.85) (Table 3).

## DISCUSSION

In this population-based cohort study of almost 800,000 children, early-life injuries were associated with a subsequent clinical diagnosis of ADHD. Having sustained at least 1 injury before age 5 resulted in a 64% higher risk of ADHD, relative to those without injuries before age 5. The association showed a dose-response pattern, as increasing number of injuries was associated with incremental increased risks of ADHD. Children with 3 or more injuries had a 2.5-fold increased risk of subsequently being diagnosed with ADHD after age 5, when compared with children without early-life injuries.

Decades of research provide strong evidence that ADHD is associated with a 39%–53% increased risk of injuries[15] and that ADHD medication reduces this risk.[13,15] ADHD is associated with more collisions when riding a bicycle, more risk-taking behavior, impulsive decision-making,[46] and, in adults, higher rates of serious traffic accidents.[47] The risk of fatal injuries is also increased in individuals with ADHD, and accidents are their most common cause of death.[48,49]

Other than symptoms of inattention, hyperactivity, and impulsivity, little is known about what characterizes children with ADHD in their first years of life, prior to being diagnosed. Some retrospective studies have found that children attending emergency wards have higher rates of ADHD symptoms than other children.[7–11] Here, we show for the first time using an objective measure that early-life injury is strongly associated with later ADHD risk and that increasing number of injures before age 5 may already be a marker of ADHD liability prior to diagnosis.

We also found familial coaggregation of injuries and ADHD, which suggests that the etiology of the 2 phenotypes includes shared familial risks. The associations were stronger

between first-degree than second-degree relatives, and in the general population, genetic liability for ADHD, as indexed by ADHD polygenic risk scores, was marginally associated with early-life injuries. However, we also found a genetic correlation of 0.53 between ADHD and early-life injuries, a higher correlation than ADHD shows with other neuropsychiatric disorders.[24,50,51] This suggests that their underlying genetic liability is partly shared. However, the SNP-based heritability of injuries was low (6%), in keeping with findings from previous twin studies that have found little evidence for a genetic contribution to injuries.[26,27] Other shared familial risks could be related the psychosocial environment in the family, which is associated with both injuries and ADHD (including, eg, family history of mental disorders,[52,53] parental unemployment,[54,55] and teenage parenthood[26,56]). Finally, our observations could also be explained by gene-environment correlation whereby genetic liability to ADHD increases the risk for environmental stressors, a phenomenon that to date has only been observed for social stressors.[57–59]

We find that the risk of injuries may be linked to individual and familial characteristics, and not merely caused by external factors, which supports a hypothesis suggested in 1919.[60] Based on that, the concept of "accident proneness" was presented in 1926.[61–63] During the 1940s and 50s, several publications supported this concept, linking it with different psychiatric symptoms, including distractibility, impulsivity, aggression, impatience, opposition, restlessness, and hyperactivity,[64,65] and also documenting familial aggregation of accidents.[66,67] Later, the concept of "accident proneness" was criticized for placing the responsibility of sustaining an injury solely on the injured individuals themselves.[68,69] While our data suggest shared liabilities for injuries and ADHD, and that individuals more prone to injuries are more likely to have ADHD, this still explains very little of the variance in early-life injuries.

Major strengths of our study include the longitudinally recorded individual-level data on a population-based national sample in a country with free universal health care. Furthermore, we were able to link the individual information with information in parents and siblings and to link with genetic information on all with an ADHD diagnosis and randomly selected controls. The randomly selected cohort enables us to present valid estimates of absolute risk in the general population, something most studies cannot do. Furthermore, our similar findings among individuals with high and low educated parents suggest that the association between injuries and ADHD is only minimally biased by differences in hospital-seeking behavior due to SES. However, our study also has some important limitations. First, we did not estimate the potentially mediating or moderating effects of other mental disorders often comorbid to ADHD (eg, conduct disorder). Second, with TBI excluded, we did not hypothesize a direct causal relationship between early injuries and ADHD, and hence we decided not to adjust analyses for, eg, parental SES or mental disorders. However, the impact of home environment, parental behavior, or parent-child interactions was not assessed, and hence we were not able to fully disentangle the genetic and non-genetic contributions to the observed association. Third, we relied on previously validated data from the national health registries on clinical diagnoses of ADHD from hospital departments, and persons diagnosed by child and adolescent psychiatrists in private practices were not included. According to Danish guidelines, inattention without hyperactivity should be coded as F98.8,[70] yet the validity of this *ICD* diagnosis in the Danish registers is not fully known.[71] However, we expect this misclassification to be non-differential by groups of injury exposure, meaning our estimates of association might be underestimated. Fourth, while BOLT-REML seems to provide robust estimates for the genetic correlation in a setting with shared controls and case-control ascertainments, the estimated SNP-based heritabilities are likely underestimated and should be interpreted with caution.[72] Finally, even in children with the most injuries, more than 90% were not diagnosed with ADHD. Hence, with such a low positive predictive value, our data do not support that obtaining information about early-life injuries should be recommended as part of the clinical assessment for ADHD, or that such information would improve diagnostic validity.

To conclude, our study adds important new findings to the literature on what characterizes children with ADHD, years before they are diagnosed, and the data suggest that early-life injuries may be an early manifestation of impairment and risks related to symptoms of ADHD. Furthermore, the observed association between early-life injuries and ADHD is partly due to shared familial and genetic risks.

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***Supplementary material:*** Available at PSYCHIATRIST.COM

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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# Supplementary Material

**Article Title:** Early-Life Injuries and the Development of Attention-Deficit/Hyperactivity Disorder

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**SUPPLEMENTARY MATERIAL**

*Appendix 1. Calculation of polygenic risk scores for ADHD (PRS-ADHD)*

The polygenic risk score for ADHD (PRS-ADHD) was calculated using both internal (to iPSYCH2012) and external SNP weights (from external GWAS summary statistics). We derived externally trained PRS-ADHD using the LDpred software, specifying an infinitesimal model.[1] SNP weights were obtained from publicly available external ADHD GWAS summary statistics (1947 trio cases and pseudo-controls, 840 case and 688 controls),[2] selecting European ancestry discovery GWAS without the iPSYCH2012 sample included. The LDPred PRS was derived for a set of genotyped SNPs (n=166 329, filtered for minor allele frequency (MAF) > 1% and missing values < 10%) overlapping between the iPSYCH2012 sample and the external GWAS summary statistics and restricted to HapMap3 variants (v1.2).

Owing to the large number of ADHD cases in iPSYCH2012, we also derived another set of internally trained PRS-ADHD in an unrelated ($\hat{\pi}$ coefficient > 0.2 using PLINK--rel-cutoff), European ancestry subset of the iPSYCH2012 sample. The internally trained SNP weights were obtained using the BOLT-LMM software.[3] We performed a mixed model prediction of ADHD (i.e. best linear unbiased prediction [BLUP]) in which genotyped SNPs in the iPSYCH sample (n = 544 758, filtered for minor allele frequency > 0.01 and SNP missing rate < 0.1) were included as random effects. Prediction effect sizes from this model take into account LD between nearby SNPs to correctly weigh their contribution to the phenotypic variance (see supplementary material of Loh et al, 2015).[3] To avoid overfitting, we used 10-fold cross-validation, training the model using 9/10ths of the data and testing it in the remaining tenth. The internally trained PRS was defined as the weighted sum of the training set prediction betas on the test set genotypes. The model was adjusted for genotyping wave, sex, age, and the first 10 principal components (PCs). The final PRS-ADHD was a linear combination of the internally and externally trained PRS variables, where the regression coefficients were inferred using two-fold cross validation on the test set. These PRS were standardized to the mean and standard deviation of the iPSYCH2012 control population.[4]

PRS were derived at the secured national GenomeDK high-performance computing cluster in Denmark and then imported to Statistics Denmark secure servers for linkage to other registry information. Further details on this procedure for PRS calculation can be found in a recently published paper.[5]

*Appendix 2. Calculation of SNP-heritability and genetic correlation*

SNP-heritability ($h^2_{SNP}$) and genetic correlation ($r_g$) between early-life injuries and ADHD were estimated using BOLT-REML software[6] among the iPSYCH2012 ADHD cases and subcohort. The sample was restricted to individuals of European ancestry based on PCA analysis.[7] Furthermore, individuals were filtered for relatedness using PLINK command --rel-cutoff 0.05.[6] Genotyped and imputed SNPs were filtered for MAF > 1%, SNP missing rate < 5% and info score > 0.8 according to BOLT-REML suggested guidelines[6]. SNPs were then LD-pruned in two rounds in PLINK version1.90[8-10] using command --indep-pairwise (50 5 0.9), resulting in a number of 785 388 SNPs used for analysis. Finally, heritability estimates were transformed to the liability scale as proposed by Lee et al.,[11] assuming population prevalence of 5% for ADHD and 10% for injuries.

*Table 1 ICD-10 codes and frequencies of types of injuries before age five in boys and girls in the study population*

| Type of injury | ICD-10 codes | Individuals with injury before age five, N (%)[a] | | |
|---|---|---|---|---|
| | | All (n=786 543) | Males (n= 401 785) | Females (n=384 758) |
| Traumatic brain injury (TBI)[b,c] | S02.0-1, S02.3, S02.7-9, S06, S07, S09.0, S09.7-9, S18, T02.0, T04.0, T06.0, T90.2, T90.5, T90.8-9 | | | |
| Any non-TBI injury[d,e] | Any of the codes below | 92 691 (11.8) | 56 660 (14.1) | 36 031 (9.4) |
| Severe and multiple injuries and traumatic amputation | S28, S38, S48, S58, S68.3, S68.4, S68.8, S68.9, S78, S88, S98.0, S98.3, S98.4, T05, T09.6, T11.6, T13.6, T14.7 | 10 (0.01) | 5 (0.0) | 5 (0.0) |
| Fracture | S02.2, S02.4-6, S12, S17, S22, S32, S42, S47, S52, S57, S62, S67, S68.0, S68.1, S68.2, S72, S77, S82, S87, S92, S97, S98.1, S98.2, T02, T04, T08, T10, T12, T14.2 | 13 479 (1.7) | 8 030 (2.0) | 5 449 (1.4) |
| Internal organs | S26, S27, S36, S37 | 48 (0.0) | 34 (0.0) | 14 (0.0) |
| Open wounds[f] | S01, S04, S05, S08, S11, S14-S16, S18, S19, S21, S24, S25, S29, S31, S34, S35, S39, S41, S44-S46, S49, S51, S54-S56, S59, S61 S64-S66, S69, S71, S74-S76, S79, S81, S84-S86, S89, S91, S94-S96, S99, T01, T06, T07, T09.1, T09.3-5, T09.8, T09.9, T11.1, T11.3-5, T11.8, T11.9, T13.1, T13.3-5, T13.8, T13.9, T14.1, T14.4, T14.5, T14.8, T14.9 | 44 393 (5.6) | 29 727 (7.4) | 14 666 (3.8) |
| Dislocation, sprain and strain | S23, S33, S43, S53, S63, S73, S83, S93, T03, T09.2, T11.2, T13.2, T14.3 | 11 239 (1.4) | 5 560 (1.4) | 5 679 (1.5) |
| Superficial injury | S00, S10, S20, S30, S40, S50, S60, S70, S80, S90, T00, T09.0, T11.0, 13.0, T14.0 | 33 902 (4.3) | 20 902 (5.2) | 13 000 (3.4) |
| Burns | T20-T31 | 2 964 (0.4) | 1 793 (0.4) | 1 171 (0.3) |
| Foreign bodies | T15-19 | 7 724 (1.0) | 4 190 (1.0) | 3 534 (0.9) |

[a] Prevalence of types of injuries do not sum to the prevalence of any injury, as individuals may have been diagnosed with several types of injuries before age five.
[b] Individuals with TBI before age five (n=22 337, 12 136 males and 9 917 females) were not included in the final study population.
[c] In parents, ICD-8 codes N800-804, 850-854 were additionally used to identify TBI.
[d] To include only unintentional injuries, any hospital contacts due to self-harm were excluded (ICD-10 code X60-X84 or reason for contact code 4). In parents, ICD-8 codes E950-959 were additionally used to identify self-harm.
[e] In parents, ICD-8 codes N805-849, 855-859 were additionally used to identify non-TBI injuries.
[f] Other and unspecified injuries are included in the category 'open wounds'.
Abbreviations: ICD-8: International classification of diseases, 8th revision, ICD-10: International Classification of Diseases, 10th revision, TBI: traumatic brain injury.

*Table 2 Inclusion criteria for study populations I-VI*

| Inclusion criteria | Excluded, N(%) | Included, N |
|---|---|---|
| Study population I: General population | | |
| All born Jan 1, 1995 - Dec 31, 2010 | | 1 191 976 |
| Born in Denmark | 144 346 (12.1) | 1 047 630 |
| Alive at age five | 3 931 (0.4) | 1 043 688 |
| Not emigrated at age five | 31 530 (3.0) | 1 012 169 |
| No diagnosis of ADHD before age five | 1 948 (0.2) | 1 010 221 |
| No prescriptions of ADHD medication before age five | 35 (0.0) | 1 010 186 |
| No diagnosis of disease of the nervous system (ICD-10: G00-G99) before age five | 15 812 (1.6) | 994 374 |
| Mother born in Denmark | 132 229 (13.3) | 862 145 |
| Farther born in Denmark | 53 549 (6.2) | 808 596 |
| No TBI before age five | 22 053 (2.7) | 786 543 |
| Study population II: Full siblings | | |
| At least one full sibling and not included in the adoption register | | 490 472 |
| Study population III: Maternal half siblings | | |
| At least one maternal half sibling and not included in the adoption register | | 57 689 |
| Study population IV: Paternal half siblings | | |
| At least one paternal half sibling and not included in the adoption register | | 54 602 |
| Study population V [a]: iPSYCH data for PRS analyses | | |
| ADHD cases and subcohort, not mutually exclusive | | 48 339 |
| Genetic information, including PRS-ADHD | 5 300 (11.0) | 43 039 |
| All born May 1, 1995 - Dec 31, 2005 | 21 904 (50.9) | 21 135 |
| Mother born in DK | 2 285 (10.8) | 18 850 |
| Father born in DK | 1 030 (5.5) | 17 820 |
| No TBI before age five | 545 (3.1) | 17 107 |
| European ancestry | 527 (3.1) | 16 580 |
| Study population VI: iPSYCH data for genetic correlations | | |
| Similar inclusion criteria as for study population V | | 16 580 |
| Unrelated individuals identified by a relatedness threshold of 0.05 as recommended for the BOLT-REML procedure.[6] | 2 247 (13.6) | 14 333 |

Abbreviations: ADHD: attention deficit hyperactivity disorder, ICD-10: International Classification of Diseases, 10th revision, iPSYCH: The Lundbeck Foundation Initiative for Integrative Psychiatric Research, PRS: Polygenic risk score, REML: Restricted maximum likelihood, TBI: traumatic brain injury.

*Table 3 Number of ADHD cases and absolute risks of ADHD by age 10 and 15 years, calculated for the entire cohort (n=22 794) and for males (n=15 994) and females (n=6 800), separately*

| | Number of incident ADHD cases | | Risk of ADHD (%) | |
|---|---|---|---|---|
| **Number of injuries** | **By age 10 years** | **By age 15 years** | **By age 10 years** | **By age 15 years** |
| All | 11 818 | 22 264 | 1.72 (1.69-1.75) | 3.33 (3.28-3.37) |
| 0 | 9 475 | 18 112 | 1.56 (1.53-1.59) | 3.05 (3.00-3.10) |
| 1 | 1 507 | 2 698 | 2.57 (2.45-2.70) | 4.87 (4.68-5.07) |
| 2 | 557 | 986 | 3.36 (3.09-3.64) | 6.31 (5.89-6.73) |
| 3+ | 279 | 468 | 4.83 (4.27-5.38) | 8.43 (7.64-9.22) |
| Males | 9 246 | 15 833 | 2.63 (2.58-2.69) | 4.79 (4.71-4.87) |
| 0 | 7 320 | 12 620 | 2.43 (2.37-2.48) | 4.43 (4.35-4.51) |
| 1 | 1 227 | 2 072 | 3.53 (3.33-3.72) | 6.46 (6.17-6.75) |
| 2 | 462 | 759 | 4.33 (3.94-4.72) | 7.53 (6.97-8.09) |
| 3+ | 237 | 382 | 6.04 (5.29-6.79) | 10.35 (9.30-11.40) |
| Females | 2 572 | 6 431 | 0.76 (0.73-0.79) | 1.81 (1.75-1.86) |
| 0 | 2 155 | 5 492 | 0.71 (0.68-0.74) | 1.69 (1.64-1.74) |
| 1 | 280 | 626 | 1.18 (1.04-1.32) | 2.56 (2.33-2.80) |
| 2 | 95 | 227 | 1.62 (1.29-1.94) | 4.11 (3.51-4.70) |
| 3+ | 42 | 86 | 2.25 (1.58-2.93) | 4.40 (3.36-5.45) |

Abbreviations: ADHD: attention deficit hyperactivity disorder.

*Table 4 Hazard ratios of different subtypes of ADHD, comparing individuals with no vs. any injuries and vs. number of injuries before age five*

| ADHD subtypes | All | | Males | | Females | |
|---|---|---|---|---|---|---|
| | ADHD cases, N | HR[a] (95% CI) | ADHD cases, N | HR[a] (95% CI) | ADHD cases, N | HR[a] (95% CI) |
| Combined subtype (F90.0) | 15688 | | 11407 | | 4281 | |
| No injuries | 12718 | 1 | 9055 | 1 | 3663 | 1 |
| >=1 injury | 2970 | 1.64 (1.57-1.71) | 2352 | 1.63 (1.56-1.70) | 618 | 1.67 (1.53-1.82) |
| Inattentive subtype (F98.8) | 4521 | | 2719 | | 1802 | |
| No injuries | 3800 | 1 | 2238 | 1 | 1562 | 1 |
| >=1 injury | 721 | 1.40 (1.29-1.52) | 481 | 1.34 (1.22-1.48) | 240 | 1.51 (1.32-1.73) |

Abbreviations: ADHD: attention deficit hyperactivity disorder, HR: Hazard ratio.

*Table 5 Association between injuries and ADHD across parental education level*

| Parental education level[a] | All | | Males | | Females | |
|---|---|---|---|---|---|---|
| | ADHD cases, N | HR[a] (95% CI) | ADHD cases, N | HR[a] (95% CI) | ADHD cases, N | HR[a] (95% CI) |
| Maternal low (n=145 728) | 8 513 | | 5 832 | | 2 681 | |
| No injuries | 6 839 | 1 | 4 564 | 1 | 2 275 | |
| >=1 injury | 1 674 | 1.48 (1.41-1.57) | 1 268 | 1.48 (1.39-1.58) | 406 | 1.49 (1.34-1.66) |
| Maternal higher (n=639 172) | 14 474 | | 10 277 | | 4 197 | |
| No injuries | 11 917 | 1 | 8 295 | 1 | 3 622 | |
| >=1 injury | 2 557 | 1.59 (1.52-1.66) | 1 982 | 1.57 (1.49-1.64) | 575 | 1.65 (1.51-1.80 |
| Paternal low (n=154 330) | 8 461 | | 5 822 | | 2 639 | |
| No injuries | 6 822 | 1 | 4 586 | 1 | 2 242 | |
| >=1 injury | 1 639 | 1.54 (1.46-1.63) | 1 242 | 1.53 (1.44-1.63) | 397 | 1.57 (1.41-1.75) |
| Paternal higher (n=627 888) | 14 286 | | 10 132 | | 4 154 | |
| No injuries | 11 738 | 1 | 8 155 | 1 | 3 583 | |
| >=1 injury | 2 548 | 1.59 (1.52-1.66) | 1 977 | 1.57 (1.50-1.65) | 571 | 1.63 (1.49-1.78) |

[a] Individuals with missing information on maternal (n=1 643, 0.2%) or paternal (n=4 325, 0.6%) education level were not included in the respective analysis.
Abbreviations: ADHD: attention deficit hyperactivity disorder, HR: Hazard ratio.

*Table 6 Familial aggregation of injuries and ADHD, with the association between parents and siblings (average) exposure to injuries and occurrence of ADHD in the index individual, estimated as hazard ratios (HR) with 95% CI*

| | All | | Males | | Females | |
|---|---|---|---|---|---|---|
| Injury exposures | ADHD cases, N | HR[a] (95% CI) | ADHD cases, N | HR[a] (95% CI) | ADHD cases, N | HR[a] (95% CI) |
| Within individual (index child) | 23 107 | | 16 191 | | 6916 | |
| No injuries | 18 850 | 1 | 12 921 | 1 | 5929 | 1 |
| >=1 injury | 4 257 | 1.61 (1.55-1.66) | 3 270 | 1.59 (1.53-1.65) | 987 | 1.65 (1.54-1.77) |
| Mothers | 23107 | | 16191 | | 6916 | |
| <2 injuries | 22706 | 1 | 15922 | 1 | 6784 | 1 |
| 2+ injuries | 401 | 1.47 (1.32-1.64) | 269 | 1.40 (1.24-1.59) | 132 | 1.65 (1.38-1.97) |
| Fathers | 23107 | | 16191 | | 6916 | |
| <2 injuries | 22467 | 1 | 15747 | 1 | 6720 | 1 |
| 2+ injuries | 640 | 1.45 (1.33-1.57) | 444 | 1.43 (1.30-1.58) | 196 | 1.47 (1.27-1.70) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Full siblings/ | 12453 | | 8926 | | 3527 | |
| No injuries | 10209 | 1 | 7291 | 1 | 2918 | 1 |
| >=1 injury | 2244 | 1.39 (1.33-1.46) | 1635 | 1.42 (1.34-1.5) | 609 | 1.33 (1.22-1.46) |
| 0 | 10209 | 1 | 7291 | 1 | 2918 | 1 |
| ]0-1] | 1691 | 1.33 (1.27-1.41) | 1213 | 1.33 (1.25-1.42) | 478 | 1.34 (1.22-1.48) |
| ]1-2] | 411 | 1.54 (1.39-1.70) | 321 | 1.71 (1.52-1.91) | 90 | 1.14 (0.93-1.41) |
| >2 | 142 | 1.81 (1.54-2.14) | 101 | 1.80 (1.48-2.19) | 41 | 1.85 (1.36-2.52) |
| Maternal half siblings | 3486 | | 2366 | | 1120 | |
| No injuries | 2633 | 1 | 1779 | 1 | 854 | 1 |
| >=1 injury | 853 | 1.28 (1.18-1.4) | 587 | 1.32 (1.20-1.46) | 266 | 1.21 (1.04-1.39) |
| Paternal half siblings | 3041 | | 2102 | | 939 | |
| No injuries | 2321 | 1 | 1616 | 1 | 705 | 1 |
| >=1 injury | 720 | 1.18 (1.08-1.29) | 486 | 1.15 (1.04-1.28) | 234 | 1.23 (1.06-1.43) |

[a] Estimates were adjusted for sex and birth year of the child, as well as the interaction between sex and birth year. Estimates of parental injury exposures were additionally adjusted for the parent's birth year. Estimates of sibling injuries were additionally adjusted for the number of siblings (full, maternal – and paternal half siblings, respectively).
Abbreviations: ADHD: attention deficit hyperactivity disorder, HR: Hazard ratio.

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