# *Correlation between epilepsy and attention deficit hyperactivity disorder a population-based cohort study*

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# Correlation between Epilepsy and Attention Deficit Hyperactivity Disorder: A Population-Based Cohort Study

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# Background

- Attention deficit/hyperactivity disorder (ADHD) A common brain disorder with onset in early childhood in widespread, but specific areas of the brain
- Frequent comorbidity with epilepsy
- Negative impact on their quality of life, significant risk factor for academic underachievement

# Epidemiology of ADHD among children with epilepsy

- ADHD in children with epilepsy: 12 to 39% in epidemiological studies (3-5% in general population ;in patients with epilepsy and overall normal IQ)
- Epidemiologic studies demonstrated an increased incidence in all kinds in children with epilepsy
- 52% had combined type, 35% inattentive type, and 13% hyperactive-impulsive type (Rhode,1999)

# Epidemiology of ADHD among children with epilepsy

| First Author, Year of Publication | Study Population | % With Hyperactivity or Combined | % With In attention |
|---|---|---|---|
| Onsted, 1955 [3] | 830 children with epilepsy | 8.4% | |
| Rutter, 1970 [4] | 64 children with epilepsy | 1.6% | |
| Holdsworth, 1974 [5] | 85 children epilepsy | 21% | 42% |
| Bravidor, 1990 [6] | 43 children <6 yr 60% intractable epilepsy | 47% | |
| Hoare, 1991 [7] | 108 children with poorly controlled epilepsy, 5-15 yr | 48% (54% parent rating scales) | |
| Dunn, 2003 [8] | 175 children with epilepsy for > 6 mo, 9-14 yr | 14% | 24% |

# Risk Factors for Inattention or ADHD in Children With Epilepsy

**Demographic factors**

- Gender: boys at increased risk—inconsistent
- Family history of ADHD—probable

**Neurologic variables**

- Learning disability or mental retardation
- Frontal lobe damage—possible association

**Seizure variables**

- Intractable seizures
- Frontal or temporal lobe focus—inconsistent
- Frequent subclinical discharges—possible

**AEDs**

- phenobarbital, benzodiazepines, topiramate, gabapentin

## Background

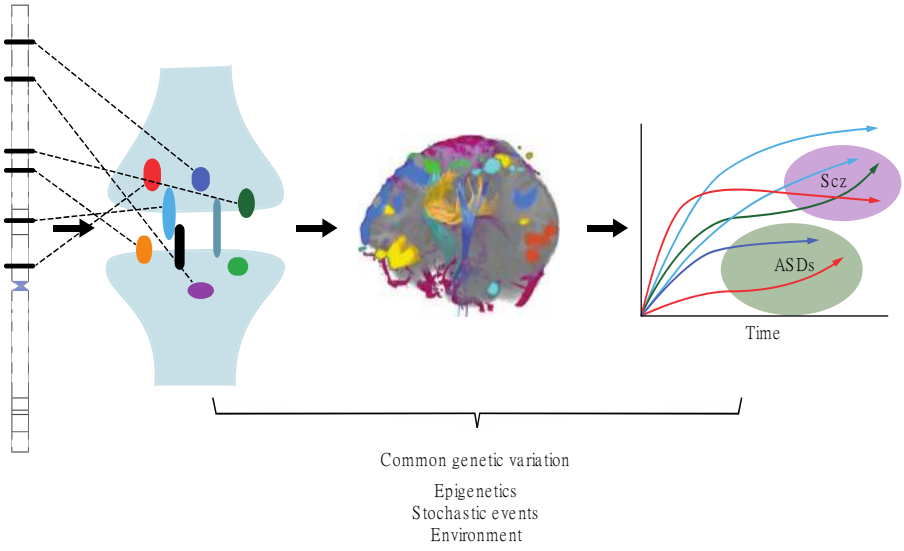
- Several factors may contribute to this comorbidity, including
  - **underlying brain pathology**
  - **chronic effects of seizures and of the epileptiform EEG discharges,**
  - **effects of antiepileptic drugs.**
  - **psychosocial factors (environment)**

## Background

- **Neurodevelopmental disorders** :

  characterized by aberrant and delayed early-life development of the brain, leading to deficits in language, cognition, motor behaviour and other functional domains, often accompanied by somatic symptoms.
- **Environmental factors**:

  increase the risk of the heterogeneous, multifactorial and polygenic disorders.




EDITORIAL

# Copy number variation in Tourette syndrome

## Another case of neurodevelopmental generalist genes?

*Neurology. 2010 May 18;74(20):1564-5.*

Jeremiah M. Scharf, MD, PhD
Carol A. Mathews, MD

Despite decades of research demonstrating that Tourette syndrome (TS) has one of the highest familial recurrence rates among non-Mendelian neuropsychiatric diseases, the search for the underlying genetic causes of TS has remained elusive. Examina-

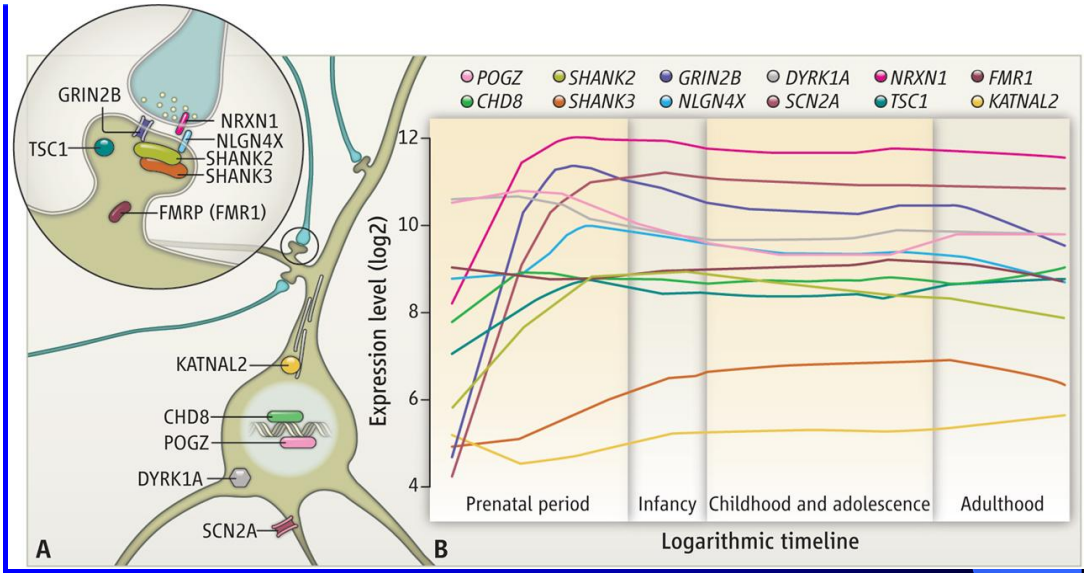
variation in TS. Using a SNP-based genotyping plat form, the authors analyzed CNV data in 111 patient with TS compared to 73 European ancestry controls Since the distinctions between normal and patho genic CNVs are still in flux[5] and the various compu

## Genetics of neurodevelopmental disorders

- The same large (100 kb) deletions/duplications present in patients with a wide range of neurodevelopmental phenotypes
- Including autism, developmental disability, schizophrenia, attention deficit hyperactivity disorder (ADHD), and seizures
- An abnormality in one gene, perhaps acting in concert with other genetic or environmental factors, could manifest in many different phenotypes

## The Genetics of Related Disorders

- Copy-number changes
  - schizophrenia
  - epilepsy
  - attention deficit–hyperactivity disorder (ADHD)
  - Autism
  - Intellectual disability
  - Tourette syndrome




- Developmental neurobiology of ASD risk genes. (A) Diverse subcellular distribution and pleiotropic roles for syndromic and idiopathic ASD proteins. (B) Expression profiles of select previously established and newly identified ASD genes during development of the human neocortex. *Science Vol 337, Sep 2012*

# Many-to-one relationship

- Gene-brain-behavior relationships
- Emergence of higher-order functions disrupted in psychiatric disorders influenced by neurodevelopmental processes guided by thousands of genes
- Organized circuitries that include sensory and motor, autonomic regulatory, social emotional and cognitive domains
- ASD has steadily increased, now reaching well into the hundreds, with no single locus accounting for more than 1% of cases.
- This suggests that future studies need to go beyond isolated molecular dissections of single mutations.

## "One-to-many" phenomenon

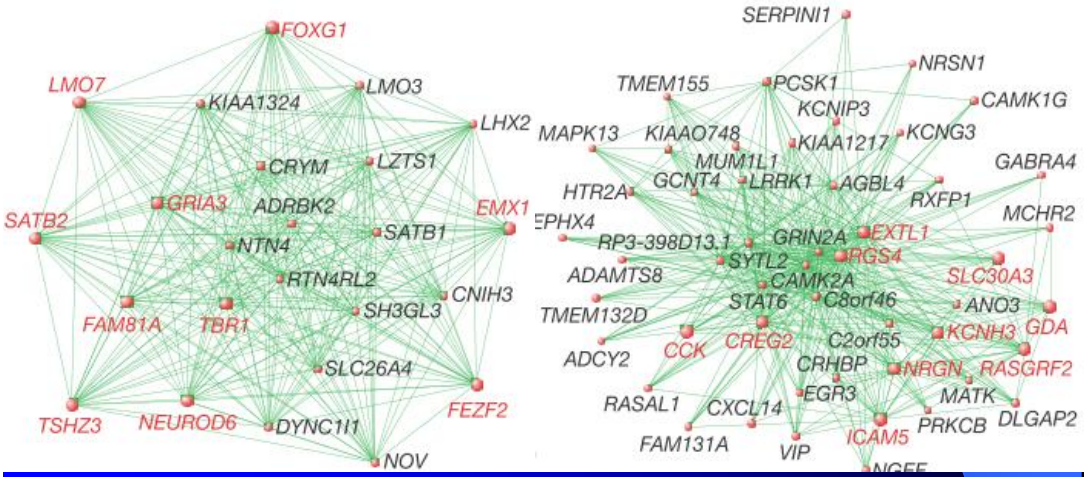
- Overlap of risks for distinct disorders.
- Identical highly penetrant variants in different individuals carry large effects but for a wide range of outcomes, including, but likely not limited to, ASD, epilepsy, intellectual disability, and schizophrenia.
- This "one-to-many" phenomenon, combined with the biological pleiotropy of genes that have so far been implicated in ASD

doi:10.1038/nature10523

# Spatio-temporal transcriptome of the human brain

Hyo Jung Kang[1]*, Yuka Imamura Kawasawa[1]*, Feng Cheng[1]*, Ying Zhu[1]*, Xuming Xu[1]*, Mingfeng Li[1]*, André M. M. Sousa[1,2], Mihovil Pletikos[1,3], Kyle A. Meyer[1], Goran Sedmak[1,3], Tobias Guennel[4], Yurae Shin[1], Matthew B. Johnson[1], Željka Krsnik[1], Simone Mayer[1,5], Sofia Fertuzinhos[1], Sheila Umlauf[6], Steven N. Lisgo[7], Alexander Vortmeyer[8], Daniel R. Weinberger[9], Shrikant Mane[6], Thomas M. Hyde[9,10], Anita Huttner[8], Mark Reimers[4], Joel E. Kleinman[9] & Nenad Šestan[1]

Brain development and function depend on the precise regulation of gene expression. However, our understanding of the complexity and dynamics of the transcriptome of the human brain is incomplete. Here we report the generation and analysis of exon-level transcriptome and associated genotyping data, representing males and females of different ethnicities, from multiple brain regions and neocortical areas of developing and adult post-mortem human brains. We found that 86 per cent of the genes analysed were expressed, and that 90 per cent of these were differentially regulated at the whole-transcript or exon level across brain regions and/or time. The majority of these spatio-temporal differences were detected before birth, with subsequent increases in the similarity among regional transcriptomes. The transcriptome is organized into distinct co-expression networks, and shows sex-biased gene expression and exon usage. We also profiled trajectories of genes associated with neurobiological categories and diseases, and identified associations between single nucleotide polymorphisms and gene expression. This study provides a comprehensive data set on the human brain transcriptome and insights into the transcriptional foundations of human neurodevelopment.




1340 samples and 16 human brain regions, 15 developmental periods, ranging from embyronic development to late adulthood

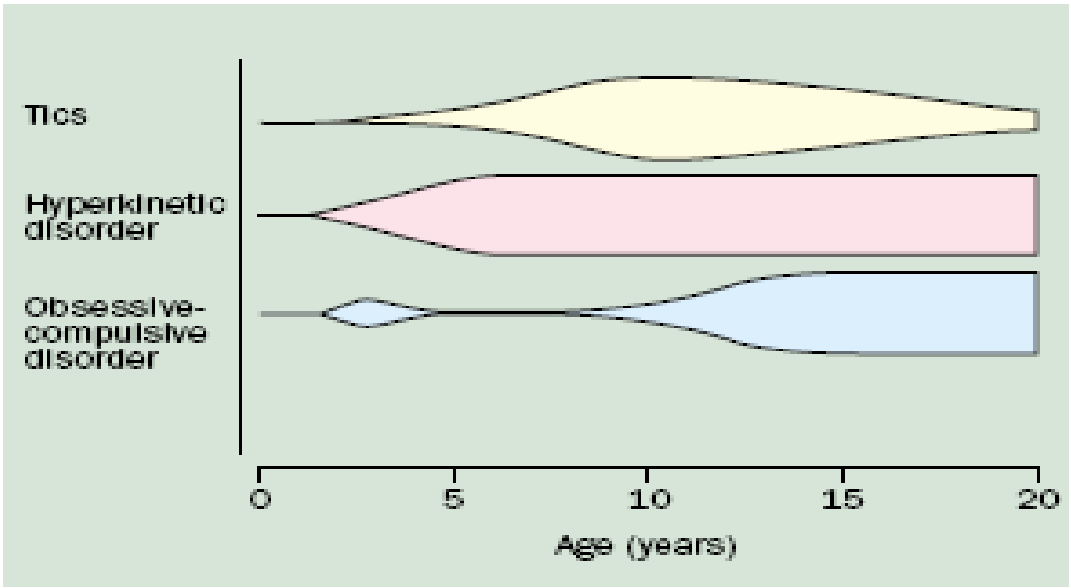



Figure 2: **Age at which tics and coexisting disorders affect patients**

Width of bars shows schematically the amount the disorder affects a

# Background

- 6.1% of ADHD abnormal EEG results; only 3.5% of healthy children (*Pediatr Neurol, 2002*).
- Children with unprovoked seizures: behavioral disturbances more common before the onset of the first seizure compared to controls *(Pediatrics, 2001*).
- 148 children with first unprovoked seizures and 89 seizure-free sibling controls: attention problems before the first seizure 2.4-fold more common in children with seizures (8.1%) than in controls (3.4%) *(Seizure, 1997)*

# Background

- Most of the previous study regarding relationship between ADHD and epilepsy were:
  - Case control study (minority)
  - Review of medical records
  - Most studies have been undertaken in clinic settings and not in large populations

# Objective

- Since there is a high association between the ADHD and epilepsy, there might be a bidirectional relationship between these two disorder.
- We performed a population-based cohort study to evaluate correlation between ADHD and epilepsy.

## Epilepsy ….. ↑ADHD

ADHD…..↑ Epilepsy

# Data source

- An electronically claims database of Taiwan National Health Insurance (NHI) program
  - covering 99% of the total 23 million population
  - contracting with more than 90% of health care facilities in Taiwan
- A subset of the longitudinal data containing randomly selected cohort of one-million insurants was used in this study.

# Study design and subjects

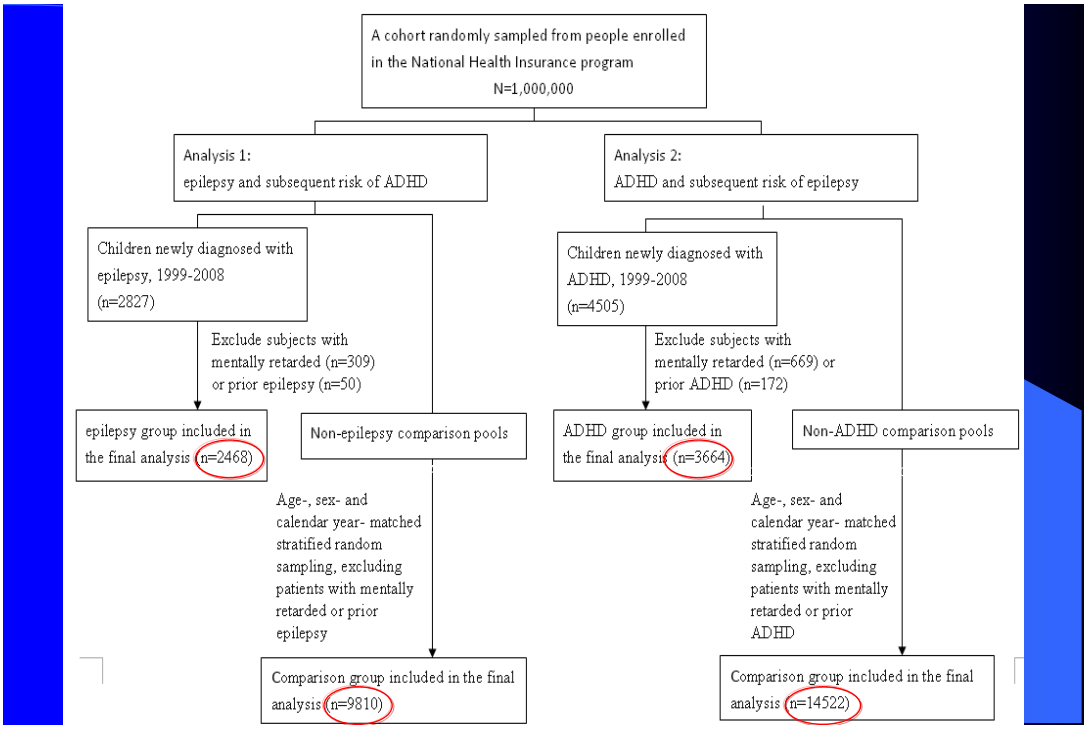
- we conducted two analysis for evaluating the bidirectional relation between
  - attention-deficit hyperactivity disorder
    - ADHD; International Classification of Disease, Ninth Revision [ICD-9], Clinical Modification, code: 314.00, 314.01
  - epilepsy (ICD-9 345) using the same procedure to select study subjects.
- Study subjects in this study were children under age 18 and without mentally retarded (ICD-9 317-319).

# Study design and subjects

- In analysis 1, we selected children newly diagnosed epilepsy during 1999-2008 and a non-epilepsy comparison group, excluding those with ADHD before.
- Analysis 2 contains children newly diagnosed ADHD during 1999-2008 and a non-ADHD comparison group, excluding those with epilepsy before.
- Index date was defined as the date of diagnosis with epilepsy (analysis 1) or ADHD (analysis2).

# Study design and subjects

- Comparison groups:
  - randomly selected
  - matched on exact age, sex and the index year
  - based on a control-to-case ratio 4.
- All patients were observed from the index date to the date of ADHD (analysis 1) or epilepsy (analysis 2), cancellation of insurance coverage, death or December 31, 2008, whichever came first.




# Analysis 1: epilepsy and subsequent risk of ADHD

- Prevalence for epilepsy: 0.34%
- The mean age was 8 years (SD 5.3 years) in epilepsy group, the same as the comparison group;
- male : female = 1.2 : 1.0
- distribution of the area : no significant difference

# Analysis 1: epilepsy and subsequent risk of ADHD

- The median follow-up
  - epilepsy group : 7.0 years
  - comparison group: 7.5 years
- The incidence of ADHD
  - Epilepsy: 7.76 per 1000 person-years (0.77%)
  - Comparison: 3.22 per 1000 person-years (0.32%)

Table 2. Hazard ratios for incidence of ADHD with epilepsy

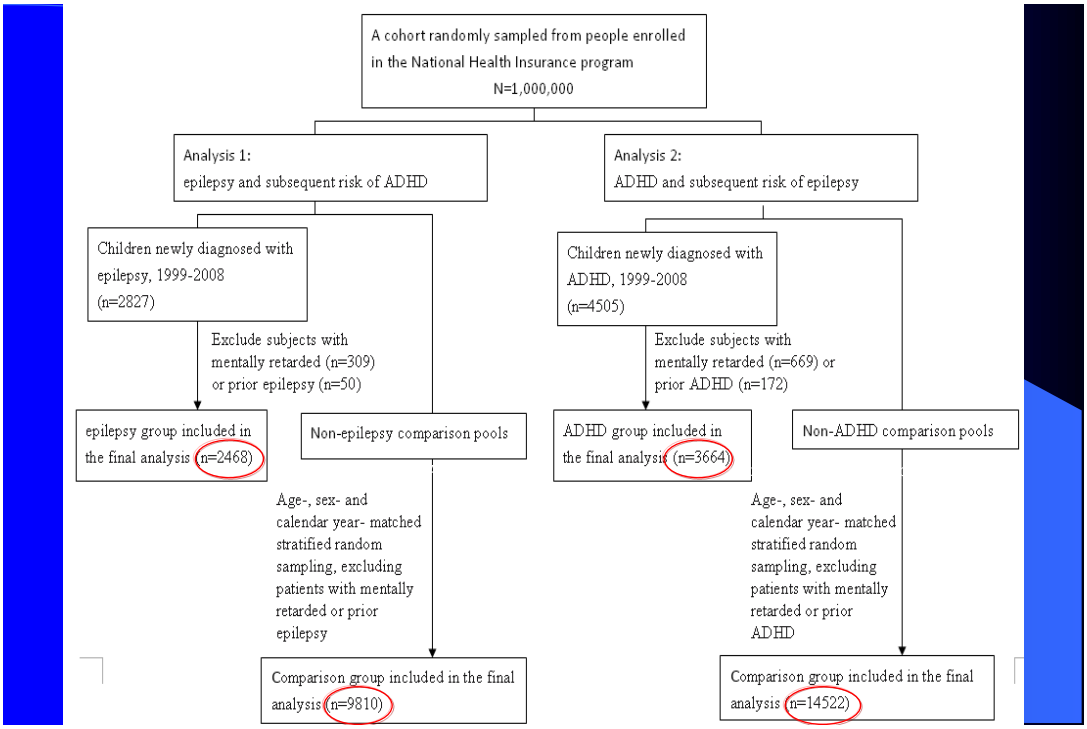
| | Hazard ratio and 95% CI (Patients with epilepsy vs. comparison group) | |
|---|---|---|
| | Unadjusted | adjusted# |
| All | 2.52 (2.01-3.17)*** | 2.54 (2.02-3.18)*** |
| Age, years | | |
| 0-6 | 2.26 (1.74-2.93)*** | 2.26 (1.74-2.94)*** |
| 6-12 | 3.50 (2.13-5.74)*** | 3.53 (2.15-5.80)*** |
| 12-18 | 5.13 (1.38-19.09)* | 5.30 (1.42-19.78)* |
| Sex | | |
| Female | 3.59 (2.19-5.86)*** | 3.59 (2.20-5.86)*** |
| Male | 2.31 (1.79-2.99)*** | 2.31 (1.78-2.98)*** |

#Adjusted for age, sex, urbanization level

PY: person-years at risk

†per1,000 person-years

*p<0.05, **p<0.01, ***P<0.0001




# Analysis 2: ADHD and subsequent risk of epilepsy

- Prevalence for ADHD: 0.5%
- The mean age was 9 years (SD 3.0 years) in ADHD group, the same as the comparison group;
- male : female = 4 : 1
- Children living in higher urbanized area had higher percentage of ADHD.

# Analysis 2: ADHD and subsequent risk of epilepsy

- The median follow-up
  - ADHD group: 3.3 years
  - comparison group: 3.5 years
- The incidence of epilepsy
  - ADHD group:3.24 per 1000 person-years (0.32%)
  - comparison group: 0.78 per 1000 person-years (0.08%)

Table 4. Hazard ratios for incidence of epilepsy with ADHD

| | Hazard ratio and 95% CI (Patients with ADHD vs. comparison group) | |
|---|---|---|
| | Unadjusted | adjusted[#] |
| All | 4.14 (2.72-6.31)*** | 3.94 (2.58-6.03)*** |
| Age, years | | |
| 0-6 | 4.09 (2.05-8.19)*** | 3.79 (1.88-7.62)** |
| 6-12 | 4.20 (2.28-7.76)*** | 4.16 (2.24-7.74)*** |
| 12-18 | 4.07 (1.43-11.62)** | 3.84 (1.32-11.14)* |
| Sex | | |
| Female | 4.47 (1.90-10.54)** | 4.44 (1.86-10.61)** |
| Male | 4.04 (2.49-6.54)*** | 3.81 (2.34-6.21)*** |

[#]Adjusted for age, sex, urbanization level

PY: person-years at risk

[†]per1,000 person-years

[*]p<0.05, [**]p<0.01, [***]P<0.0001

# Discussion

- *Analysis 1: epilepsy and subsequent risk of ADHD*
  - Our sample (general population)
    - male : female = 1.2/1.0 (no difference)
    - Prevalence of epilepsy = 0.34% (0.5-1%)

# Analysis 1: epilepsy and subsequent risk of ADHD

- Previous retrospective studies :
  - Children with epilepsy have a significant risk for ADHD, a prevalence of 12–39% ,
  - general pediatric population: 3-7%
- the incidence of ADHD
  - Epilepsy: 7.76 per 1000 person-years (0.77%)
  - Comparison: 3.22 per 1000 person-years (0.32%)
- Children with epilepsy had higher risk of developing ADHD
  - adjusted HR=2.54, 95% CI=2.02-3.18

# Discussion

- *Analysis 2 : ADHD and subsequent risk of epilepsy*
  - Our sample (general population)
    - male : female = 4:1 (5:1)
    - Prevalence of ADHD = 0.5% (3-7 %)

# Discussion

- *Analysis 2 : ADHD and subsequent risk of epilepsy*
  - **population-based case-control study (n=109):**
    - **A history of ADHD was 2.5-fold more common among children with newly diagnosed seizures**
    - **The association was restricted to ADHD predominantly inattentive type (odds ratio [OR], 3.7; 95% CI, 1.1-12.8),**
    - **not ADHD predominantly hyperactive-impulsive type (OR, 1.8; 95% CI, 0.6-5.7) or**
    - **ADHD combined type (OR, 2.5; 95% CI, 0.3-18.3).**

***Pediatrics 2001***

# Analysis 2: ADHD and subsequent risk of epilepsy

- The incidence of epilepsy
  - ADHD group:3.24 per 1000 person-years (0.32%)
  - comparison group: 0.78 per 1000 person-years (0.08%)
- Children with ADHD had higher risk of developing epilepsy
  - adjusted HR=3.94,

# Discussion

- *Epileptic seizures can, by themselves, cause or aggravate ADHD*
  - Epilepsy-induced impairment of networks
- *ADHD and epilepsy*
  - *a common underlying causative factors,*
    - *including genetics and environmental factors*
  - *leading to a cascade of transcriptional changes in the brain (plasticity, apoptosis, neurogenesis)*
  - *alters behavior or cognition prior to the appearance of seizures.*

# Discussion

- **Limitation of our study:**
  - Which type of ADHD had higher risk of developing epilepsy is unknown
  - Diagnoses of ADHD using standard diagnostic criteria? underdiagnosis?
  - Factors other than mental retardation, e.g cerebral palsy, predicting attention problems were not excluded
  - Influence of AEDs/ADHD medication on subsequent seizure or inattention were not excluded

# Discussion

- Are the child's seizures adequately controlled?
- EEG monitoring: determine the presence of unrecognized seizure (particularly inattention , the predominant symptom)
- Subclinical EEG subtle effect: still controversial
- AED side effect: particularly on phenobarbital, benzodiazepines, gabapentin or topiramate
- Treatment with stimulant medication in most children with ADHD

# Conclusion

- Early identification of ADHD and epilepsy comorbidity is crucial .
- Pediatrics neurologist should look for temporal relationships between the course of the epilepsy, and the onset of ADHD
- In children with epilepsy, might need drugs combination to improve long-term cognitive and behavioral prognosis.

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**Thanks for Your Attention !!**