Comorbid conditions in (adult) ADHD
From epidemiology to molecular mechanisms

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Norsk oppsummering:

- ADHD er en «utelukkelsesdiagnose»
  - Mange av symptomene er uspesifikke
- Behov for detaljert utredning
  - For differensialdiagnoser (psykiatri eller somatikk)
  - For å påvise komorbide tilstander
  - Stor betydning for å planlegge riktig behandling
- Komorbiditet kan studeres på mange ulike nivåer:
  - Befolkninger (registerstudier)
  - Pasientgrupper (kliniske studier)
  - Biomarkører
  - Mekanistisk (dyremodeller, cellulære studier molekyler)
- Særlig de genetiske biomarkører tyder på overlappende mekanismer
- Immunologiske mekanismer ved nevropsykiatriske lidelser?
- Overføring av behandlinger på tvers av komorbide tilstander («repositioning/repurposing of drugs»)?
- Nødvendig med mer translasjonell og interdisiplinær forskning
Defining Comorbidity: Implications for Understanding Health and Health Services


- “Health care increasingly needs to address the management of individuals with multiple coexisting diseases, who are now the norm rather than the exception.
- In the United States, about 80% of Medicare spending is devoted to patients with 4 or more chronic conditions, with costs increasing exponentially as the number of chronic conditions increases.
- This realization is responsible for a growing interest on the part of practitioners and researchers in the impact of comorbidity on a range of outcomes, such as mortality, health-related quality of life, functioning, and quality of health care.”

Comorbidity is common in psychiatry and somatic illness.
Outline of talk

• Background and terminology;
  – “Comorbid” can be medical condition(s) existing simultaneously but independently; or can indicate related conditions
• ADHD symptoms are not specific:
  – are observed in several somatic & psychiatric conditions:
  – ADHD considered an “exclusion diagnosis”
  – misdiagnosis or missed (additional) diagnoses?

• A systematic literature study from 1994-2015 (4091-128 references)
• Epidemiology
• Clinical case studies
• Biomarkers, including DNA variants
• Implications for diagnosis or treatment
Risk of overestimation of comorbidity?

- Artificial comorbidity due to overlapping criteria?
- Risk of selection bias: Berkson's bias, clinical selection bias?

Overlapping Phenotypes of Psychiatric Disorders

Problems with categorical diagnoses (ICD og DSM):
Borders between diagnoses og normality and disease/disorder/illness?

Clinical assessment and diagnosis of adults with attention-deficit/hyperactivity disorder

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Attention-deficit/hyperactivity disorder (ADHD) is a prevalent disorder in adult psychiatry, particularly in out-patient settings. There are no objective, laboratory-based tests that can establish this diagnosis. Present diagnostic criteria for ADHD are formulated primarily according to behavior in childhood, based on age inappropriate and impairing levels of hyperactivity, impulsivity and inattention. Other symptoms, such as mood instability and frustration intolerance, are not included in current criteria for ADHD, but are very prevalent in this patient group. ADHD is often comorbid with alcohol and substance abuse and other psychiatric disorders, in particular anxiety and personality disorders. Thus, the diagnostic assessment should both include a comprehensive clinical interview, rating scales for past and present symptoms and collateral information from multiple informants, as well as assessment of a broader spectrum of psychiatric and somatic conditions. As ADHD is associated with changes in brain function mediating different aspects of neuropsychological functions, assessment of those functions is important to understand the symptom patterns and to develop targeted treatment programs. Some topics for further research and for future developments of diagnostic criteria and tools are highlighted.

Keywords: assessment • comorbidity • diagnosis • mood instability • neuropsychology • persistent ADHD

Being a prevalent condition in both child, adolescent and adult psychiatry [1,5,8], particularly in out-patients settings, clinicians will frequently be asked to assess and treat adults with ADHD. The frequency of ADHD is high in adult psychiatry, and the condition is often comorbid with alcohol and substance abuse and other psychiatric disorders, in particular anxiety and personality disorders. Thus, the diagnostic assessment should both include a comprehensive clinical interview, rating scales for past and present symptoms and collateral information from multiple informants, as well as assessment of a broader spectrum of psychiatric and somatic conditions.
Checklists / systematic interviews, examinations and laboratory tests to determine:

Are symptoms better explained by other psychiatric or somatic conditions?

Does the patient suffer from concurrent medical conditions (psychiatric or somatic comorbidity)?

Causally related to ADHD or unrelated?

What are the implications of these conditions for future management/ treatment?

Secondary ADHD?

Haavik et al. Exp. Reviews 2010
Adult ADHD and Comorbid Somatic Disease: A Systematic Literature Review

Johanne Telnes Instanes¹,²,³, Kari Klungsøy⁴, Anne Halmøy¹,³,⁵, Ole Bernt Fasmer⁶, and Jan Haavik¹,³,⁵

Abstract
Objective: To systematically review, synthesize, and appraise available evidence, connecting adult ADHD (aADHD) with somatic disease. Method: Embase, Psychinfo, and Medline databases were searched for studies published from 1994 to 2015 addressing aADHD and somatic comorbidity. Somatic conditions were classified according to International Classification of Diseases (ICD-10) codes. Levels of evidence were graded as inconclusive, tentative, or well documented. Results: Most of the 126 studies included in the qualitative synthesis were small and of modest quality. Obesity, sleep disorders, and asthma were well-documented comorbidities in aADHD. Tentative evidence was found for an association between aADHD and migraine and celiac disease. In a large health registry study, cardiovascular disease was not associated with aADHD. Conclusion: There are few large systematic studies using standardized diagnostic criteria evaluating aADHD and somatic comorbidities. Significant associations are found between aADHD and several somatic diseases, and these are important to consider when assessing and treating either aADHD or the somatic diseases. (J. of Att. Dis. XXXX; XX(X) XX-XX)

Keywords
adult ADHD, asthma, migraine, sleep disorders, review
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*The reported studies were classified into conditions: the association between ADHD and the somatic disease is well established (i), preliminary evidence for association conditions where evidence is still incomplete (ii), and no conclusion (iii).*
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<td>Enuresis.</td>
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</table>

<sup>a</sup>The reported studies were classified into conditions: the association between ADHD and the somatic disease is well established (i), preliminary evidence for an association, conditions where evidence is still too weak to make conclusions (iii). <sup>b</sup>Conflicting evidence. One study shows no association, another study shows shows association.
Sleep & ADHD

Bergen insomnia scale (BIS)

1. Has it taken you more than 30 minutes to fall asleep after the light was switched off?
2. Have you been awake for more than 30 minutes between periods of sleep?
3. Have you awakened more than 30 minutes earlier than you wished without managing to fall asleep again?
4. Have you felt that you have not had enough rest after waking up?
5. Have you been so sleepy/tired that it has affected you at school/work or in your private life?
6. Have you been dissatisfied with your sleep?

Insomnia was far more frequent among adults with ADHD (66.8%) than in the population controls (28.8%) \( (P < 0.001) \).

Insomnia was more common in adults with the combined subtype than in those with the inattentive subtype (79.7% and 55.6%, respectively) \( (P = 0.003) \).

For self-reported current ADHD symptoms, inattention was strongly correlated to insomnia.

Patients currently using stimulant treatment for ADHD reported a lower total insomnia score compared to patients without medication \( (P < 0.05) \).

Brevik et al., Acta Psychiatrica Scandinavica 2017
Psychiatric comorbidity in Norwegian adults with ADHD (Solberg et al., submitted)

<table>
<thead>
<tr>
<th></th>
<th>ADHD %</th>
<th>Comparison group %</th>
<th>P-value</th>
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<tr>
<td><strong>Number N (% females)</strong></td>
<td>2.1</td>
<td>97.9</td>
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<td>31,190 (44.8)</td>
<td>1,488,348(49.0)</td>
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<td><strong>Mean age (yrs)</strong></td>
<td>29.3</td>
<td>31.8</td>
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<td><strong>Socioeconomic status</strong></td>
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<td>Low</td>
<td>35.3</td>
<td>27.0</td>
<td>&lt;0.0001</td>
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<td><strong>Maternal marital status</strong></td>
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<tr>
<td>Single</td>
<td>16.9</td>
<td>9.5</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Maternal/paternal psychiatric disorders</strong></td>
<td>18.9/11.6</td>
<td>7.8/5.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Sex Differences of Psychiatric Comorbidity in Adult ADHD
Berit S. Solberg, Anne Halmøy, Jan Haavik, & Kari Klungsøyr, (submitted)
Conclusions

- 4-8 X increased risk for anxiety, depression, SUD, personality disorders and psychosis in adults with ADHD

- No gender differences for comorbidity, except for increased risk for anxiety and depression in males

- Females relative to males
  - ↓ risk for SUD and psychosis
  - ↑ risk for anxiety, depression bipolar and personality disorders regardless of ADHD or not
Maternal chronic inflammatory disease & offspring ADHD. Offspring of mothers with rheumatoid arthritis or asthma: 20-80% increased risk of ADHD

Attention-deficit/hyperactivity disorder in offspring of mothers with inflammatory and immune system diseases. Instanes et al. Biological Psychiatry 2015
ADHD cases

• Norwegians born 1967 – 2008: \( N = 48,396 \)
  – dispensed central stimulants (CS) or atomoxetine 2004 –12,
  – age ≥ 4 years
  – excluded if narcolepsy

• 4 – 17 years (children); \( N = 27,358 \)
  – 18 - 46 years (adults); \( N = 21,038 \)

Controls

• All remaining individuals in the MBRN born 1967-2008 and surviving 4 first years

• \( N = 2,326,420 \)

• Young control group: Born > 1985

• Adult control group: Born < 1995

Instanes et al. Biological Psychiatry 2015
Pre- and Perinatal Risk Factors in Adults with Attention-Deficit/Hyperactivity Disorder

Anne Halmøy, Kari Klungsøy, Rolf Skjæven, Jan Haavik

Received 13 May 2011; received in revised form 15 November 2011;

Background
Attention-deficit/hyperactivity disorder (ADHD) is a prevalent and lifelong disorder for ADHD persisting beyond adolescence. The present study investigated perinatal complications and ADHD in adulthood.

Methods
We used data from the Medical Birth Registry of Norway to compare the prevalence of ADHD, with the remaining population born in 1973–2000 (N = 1,170,073). Relative risks (RR) adjusted for potential confounders were calculated.

Results
Preterm (< 37 weeks of gestation) and extremely preterm birth (< 28 weeks) were associated with increased risks of ADHD, respectively. Birth weights <2500 g and <1500 g were also significant risk factors.

Relative risk of adult ADHD (18-40 years), as a function of gestational age at birth (N= 2323 vs. 1.17 million)
ADHD has a high heritability.

Glatt et al. (2008), “Psychiatric Genetics: A Primer,” in J. Smoller et al. (Eds.), Psychiatric Genetics: Applications in Clinical Practice (pp. 3-26).
ADHD genetics

- «Mendelian» syndromes with ADHD-symptoms
- One or few risk genes
- «Easy» to find genes

- «Common» ADHD
- Many risk variants
- Small effects
- Difficult to «prove»
Genetics

- Polygenic risks for many common multifactorial traits/disorders
- SNP co-heritability can be used to study genetic overlap between traits
- Elucidation of shared genetic mechanism for comorbid conditions could lead to new therapies or diagnostic procedures

PGC cross disorder group. Lancet 2013; 381: 1371–79
Genetic overlap between neuropsychiatric disorders

Anttila et al (2016)
http://dx.doi.org/10.1101/048991

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; MDD – major depressive disorder; OCD – obsessive-compulsive disorder.
Figure 3. Genetic correlation matrix across neurological and psychiatric phenotypes.

Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder.

Anttila et al (2016)
http://dx.doi.org/10.1101/048991
Genetic overlap with sociodemographic and other traits

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<th>OCD</th>
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<th>Focal epilepsy</th>
<th>Generalized epilepsy</th>
<th>ICH</th>
<th>Ischemic stroke</th>
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Color of each box indicates the magnitude of the correlation, while size of the boxes indicates its significance, with significant correlations filling each box completely. Asterisks indicate genetic correlations which are significant after Bonferroni correction. ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; ICH – intracerebral hemorrhage; MDD – major depressive disorder; OCD – obsessive-compulsive disorder; BMI – body-mass index.

Anttila et al (2016)
Nutrition as explanation for comorbidity in ADHD?

Vitamin levels in adults with ADHD

Elisabeth Toverud Landaas, Tore Ivar Malmei Aarsland, Arve Ulvik, Anne Halmøy, Per Magne Ueland and Jan Haavik

Background
Micronutrients containing vitamins are reported to reduce symptom levels in persons with attention-deficit hyperactivity disorder (ADHD), but data on vitamin levels in ADHD are sparse.

Aims
To examine the relationship between vitamin concentrations, ADHD diagnosis and psychiatric symptoms in young adult ADHD patients and controls.

Method
Eight vitamins and the nicotine metabolite cotinine were analysed in serum samples from 133 ADHD patients and 131 controls aged between 18 and 40, who also reported ADHD symptoms and comorbid conditions.

Results
Lower concentrations of vitamins B2, B6 and B9 were associated with the ADHD diagnosis, and B2 and B6 also with symptom severity. Smokers had lower levels of vitamins B2 and B9.

Conclusions
ADHD patients were overrepresented in the group with low levels of some vitamins, possibly indicative of inadequate dietary intake of these micronutrients in a subgroup of patients. It is important to identify these patients in dietary intervention trials of ADHD.

Declaration of interest
J.H. has received lecture honoraria as part of continuing medical education programmes sponsored by Novartis, Eli Lilly and Company, and Janssen-Cilag.

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A subgroup of adult ADHD patients have low levels of vitamins A, B2, B6, B9 and D

Landaas et al (2016)

A subhgroup of adult ADHD patients have low levels of vitamins A, B2, B6, B9 and D. Landaas et al (2016)
Conclusions & Implications for diagnosis and treatment:

• Detailed psychiatric & somatic assessments are needed
  – for differential diagnosis
  – to reveal comorbid conditions

• Different research designs to study comorbidity: population, clinical, cellular or molecular levels.

• Biomarkers can reveal shared etiopathogenic pathways
  – Overlapping polygenic contributions to many psychiatric and somatic disorders/diseases
  – Some serum biomarkers, including immunological markers have indicted autoimmune mechanisms in ADHD

• Repositioning of previously drugs therapies are being investigated in ADHD

• More translational / cross disciplinary research is needed
Acknowledgments

2013-2018
ECNP Network

2015-2018
MiND

2015-2018
ADHD & MIND TRAIING NETWORK

2016-2020
E2BN 2017-2021

K.G. JEBSEN
Center for Medical Research

HORIZON 2020

CoCA
ADHD COMORBIDITY

Framwork Programme for Research and Innovation

ECNP Network
ADHD across the Lifespan

Seventh Framework Programme