Epidemiology of adult Attention Deficit Hyperactivity Disorder (ADHD)

Thesis

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List of Abbreviations

ADD – Attention Deficit Disorder

ADHD – Attention Deficit Hyperactivity Disorder

ARS – ADHD Rating Scale

ASRI-4 – Adult Self-Report Inventory-4

ASRS – Adult ADHD Self-Report Scale

CASI – Current ADHD Symptom Interview

CBCL – Child Behavior Checklist

CI – Confidence Interval

Comb. -ADHD Combined type

CPRS-R – Revised Conners Parent Rating Scale

CSS – Current Symptoms Scale

DCD – Developmental Coordination Disorder

DRC - Developmentally Referenced Criterion

DSM – Diagnostic and Statistical Manual of Mental Disorders

GLM – General Linear Model

GP – General Practitioner

HI - ADHD Hyperactive/Impulsive type

HSQ – Home Situation Questionnaire

I – ADHD Inattentive type

ICC – Intra-class Correlation Coefficient

LL – Log Likelihood

M – Mean

M.I.N.I. – Mini International Neuropsychiatric Interview

M-NCS – Mexican National Comorbidity Survey

N – sample size

NCS-R – National Comorbidity Survey Replication

NHA-2 – Nijmegen Health Area Study - 2

ODD – Oppositional Defiant Disorder

OR – Odds Ratio

P – estimated proportion of cases

POS – proportion of positive cases

$PREV_p$ – true population prevalence

SAS – Statistical Analysis System

SD – Standard Deviation

SE – Standard Error

Se – Sensitivity

Sp - Specificity

WHO – World Health Organization

WURS – Wender Utah Rating Scale

WWPARS – Werry-Weiss-Peters Activity Rating Scale

Y – Year

YARS – Young Adult Rating Scale

1. Introduction

ADHD is one of the most frequent psychiatric conditions in childhood. The main features – the so called „core symptoms" – of ADHD are inattention, hyperactivity and impulsivity. According to the estimations published in the literature, ADHD affects 3-9% of school age children (1). ADHD in adults became the focus of research in the past two decades. During this time, the results of follow-up studies proved that ADHD is not only a childhood condition, but persists into adulthood in a high proportion of cases (2-8). The validity of the diagnosis of ADHD in adults was further supported by findings of imaging studies, reporting on several structural and functional brain abnormalities similar to those found in children with ADHD (9-15); findings of neuropsychological studies showing congruent dysfunctions with the brain abnormalities reported in imaging studies and similar to those reported in children (14;16-23); as well as reports on the therapeutic efficiency of stimulants, specifically used for the pharmacotherapy of ADHD both in children and in adults (24-28).

The pertinent literature consistently supports the notion that ADHD in adults is associated with poor socioeconomical outcome and serious functional impairments. In particular, ADHD was associated with lower levels of education, higher rates of divorce, shifting jobs, unemployment and criminality, higher frequency of overspeeding and car accidents, higher rates of sexually transmitted diseases and accidents in general, lower self-esteem, lower level of self-care (29-34). Moreover, ADHD was shown to be also a serious risk factor for psychiatric comorbidity. Personality disorders, especially antisocial personality disorder, substance abuse and dependency, affective and anxiety disorders were reported consistently as the most frequent comorbid conditions with ADHD in adults (6-8;35-37).

ADHD in adults, due to the high level of criminality and unemployment represents serious burden on the society with significant economical consequences, beyond its obvious effect on the health care system and the individual's life. Kessler et al (29), based on the results of the National Comorbidity Survey Replication estimated 19.5 billion USD/year cost of ADHD in the US due to missing labor days. Birnbaum et al (38) reported on a total of 31.6 billion USD/year cost of ADHD including treatment costs of people with ADHD and relatives of people with ADHD, all other healthcare

costs of people with ADHD and their relatives, and workloss costs. According to an estimation in Germany based on the 2002 data of the Federal Office of Statistics, direct costs of hyperkinetic disorder and ADHD was 142 million Euro/year (39).

1.1 Symptoms of adult ADHD

ADHD is charactarized by three core symptoms: inattention, hyperactivity and impulsivity. Inattention implies distractibility, difficulties or impossibility of focusing and sustaining attention which result in lots of mistakes at work, losing details, avoiding those activities where focusing is needed. People with ADHD have difficulties in managing their everyday life, they are disorganised, forgetful and frequently losing things. Because they might seem they do not pay attention at all to others and they keep on forgetting important dates, tasks or requests, their relationships are ususally complicated and are full of with conflicts, not only in their private life but in their working environment as well.

Hyperactivity among adults mainly appears as restlessness. People with ADHD are always „on the go", typically cannot sit still, are fidgeting most of the time and usually talk too much. Impulsivity mainly shows as being impatient, losing temper, „talking before thinking", interrupting others when talking, making decisions without judging their possible consequences.

Beside these core symptoms there are certain features of adult ADHD which overlap with other psychiatry conditions/disorders making the correct diagnosis difficult. Some of these features are for example: procrastination, sleep disturbances, mood swings, emotional lability, tantrums (40-42).

1.2 Diagnosis of adult ADHD

To date there are no validated, clear diagnostic criteria for adult ADHD. The reason for this scarcity can partially be explained by the fact that up till the early 80's ADHD was considered to be a disorder of childhood. Below I present the main stages of the development of ADHD diagnostic criteria and the approach to the adult form of the disorder.

1.2.1. The Utah criteria

Wender and collegues published the first results on a small cohort of adults who were diagnosed with ADHD like symptoms in childhood („minimal brain damage" according to the diagnostic nomenclature in those days). Wender prescribed psychostimulants to these adults with reasonable therapeutic effect, hence facilitating the research into adult ADHD. According to Wender:

„ADHD is probably the most common chronic undiagnosed psychiatric disorder in adults. It is characterized by inattention and distractibility, restlessness, labile mood, quick temper, overactivity, disorganization, and impulsivity. It is always preceded by a childhood diagnosis, a disorder that is rarely inquired about and usually overlooked." (43)

It was also Wender, who first questioned the developmental appropriateness of the Diagnostic and Statistical Manual of Mental Disorders (DSM) system's approach towards ADHD in adults and created an independent diagnostic system, based on his empirical work (43;44). According to this system, during the diagnostic process not only the patient but an additional informant, preferably a parent, had to take part in the interview to assess retrospectively the childhood diagnosis of ADHD. Evidence for ongoing, continued impairment from hyperactive and inattentive symptoms was also obtained. Wender suggested seven symptom clusters to characterize the phenomenology of adult ADHD:1) inattentiveness, 2) hyperactivity, 3) mood lability, 4) irritability and hot temper, 5) impaired stress tolerance, 6) disorganization, and 7) impulsivity. The Utah criteria for adult ADHD required a retrospective childhood diagnosis, ongoing difficulties with inattentiveness and hyperactivity, and at least two of the remaining five symptoms (43;44). For assisting to the retrospective diagnosis of childhood ADHD the Wender Utah Rating Scale was developed (45). This scale is a self-report measure of retrospective childhood behavioral symptoms.

The Utah criteria introduced the necessity of retrospective childhood diagnosis and the third party informant on behavioral symptoms which are both important parts of the current clinical practice in the diagnosis of ADHD in adults. Furthermore, Wender's finding played a key role in the acknowledgment of adult ADHD both in scientific and clinical work. Nevertheless, the Utah criteria has its limitations as well. First, since it

requires both hyperactivity and attentional difficulties, the Utah criteria excludes those individuals who have serious impairments but only predominantly inattentive symptoms. Second, with the development of the DSM system the Utah criteria became more and more divergent from the actual conceptualization of adult ADHD. Although Utah citeria and the WURS were applied in numerous previous studies, by now it is difficult to compare results across studies that used either the DSM or the Utah criteria for the diagnosis. Third, based on several validation field trials among children and adolescents, hot temper, irritability and mood lability were shown to be associated with different outcome and impairments from the other symptoms, and were more closely linked to environment and socialization factors. Moreover, these symptoms significantly overlap with different other psychiatric disorders (bipolar disorder, major depression, oppositional defiant disorder, conduct disorder etc.) thus, denoting serious confounding factors in the diagnostic process. The Utah criteria also excludes those individuals with ongoing major depressive episode, psychotic disorder or severe personality disorder. This latter criterion is useful in research work, especially when investigating the effect of therapeutic approaches, or neuropsychological, structural or functional brain abnormalities in the background of ADHD, but hinder the application of the Utah criteria in the everyday clinical practice as well as in epidemiologic studies since it exludes those individuals with comorbid psychiatric conditions (44).

1.2.2. Diagnostic criteria according to the DSM system

Before and during the time of the publication of the first version of the DSM the typical syndrome of inattention and hyperactivity was considered as „minimal brain dysfunction" or „minimal brain damage" (42;46).

In DSM-II „Hyperkinetic Reaction of Childhood" diagnosis was applied and hyperactivity was considered as the dominant symptom of the disorder (47).

This concept changed in DSM-III in which inattention became the dominant symptom and the disorder was called „Attention Deficit Disorder (ADD) with or without Hyperactivity". Beside the main diagnostic categories DSM-III included for the first time a special diagnostic category for adolescents and adults who were diagnosed in childhood with ADD and continued to show inattentive and/or hyperactive/impulsive

symptoms with clinically significant functional impairment. This category was called „Attention Deficit Disorder, residual type" (48).

The currently used name of the disorder, ADHD, was first introduced in DSM-III-R which diagnostic system focused again more on the hyperactive symptoms (49).

DSM-IV applies the following diagnostic criteria: at least 6 symptoms out of the 9 inattentive symptoms and/or 6 symptoms out of the 9 hyperactive(6)/impulsive(3) symptoms have to be present in the past 6 months to a degree that is maladaptive and inconsistent with the developmental level. Some of these symptoms had to cause impairment and to be present already before the age of 7. Symptoms have to result in impairment at least in two different settings (home, school/work). There has to be clinically significant impairment in social, academic, or occupational functioning (40).

DSM-IV differentiates 3 subtypes of ADHD: (1) predominantly inattentive type; (2) predominantly hyperactive/impulsive type; (3) combined type (40).
DSM-IV also applies a category for mainly adolescents and adults who met the criteria for ADHD in childhood and continued to have significant symptoms and impairment that fell below the threshold for the full diagnosis: "attention deficit hyperactivity disorder, in partial remission". An additional category is "attention deficit hyperactivity disorder, not otherwise specified" which is used when patients have impairment from symptoms of inattention or hyperactivity/impulsivity but fail to meet the criteria for ADHD (40).

Although DSM-III-R and DSM-IV permits the diagnostic possibility for adults, these diagnostic categories have no clear and validated criteria, furthermore the diagnostic criteria detailed above was only validated among children and adolescents (44). According to McGough and Barkley (44), based on their detailed review of diagnostic controversies in adult ADHD: „DSM-IV criteria are overly restrictive and fail to identify significant numbers of adults who suffer meaningful levels of dysfunction". These authors based this statement on three main issues concerning the DSM-IV criteria. First, based on reported results in the literature, the symptom threshold applied in childhood (6 symptoms have to be present out of nine) indicated 2 to 4 Standard Deviation (SD) above the mean when applied in adults, hence, a high number of individuals, with serious impairments failed to meet the diagnostic threshold. Second, onset criteria was also criticized since it lacks empirical evidence, and there are

several practical difficulties in demonstrating impairments due to behavioral symptoms at, or before the age of 7. Additionally, when the diagnosis of adult ADHD is mostly based on self-report, it is problematic to require from adults to be able to recall precisely their symptoms from such an early age. Some authors already suggested to modify the age of onset criterion from 7 to 12 (or even 15) years of age, which notion was also supported by the DSM field trials (among children and adolescents), indicating that all of those subjects who were diagnosed with ADHD developed their disorder by the age of 12 (44;50). Third, McGough and Barkley emphasized that 'impairment' as an important criterion in the diagnosis was neither determined according to an adult's roles and functions, nor defined appropriately in the DSM system. Nevertheless, these auhors raised the possibility that with regard to Criterion E ("The symptoms...are not better accounted for by another mental disorder.") DSM might carry an „over-inclusive" feature, since DSM symptoms of ADHD include items which might overlap with other mental disorders. Taking into consideration the high proportion of comorbid mental disorders found in numerous studies when investigating adult ADHD based on DSM-IV criteria, and the lack of validation of the DSM criteria among adults, it can not be assured that DSM symptoms have the potential to properly differentiate ADHD from other mental disorders in adults (44).

1.3. Epidemiological studies of adult ADHD

In spite of the growing literature dealing with the background and the consequences of adult ADHD (9;14;15;17;21;29;31;51), as well as the effect of different therapeutic approaches (24;52;53), there is relatively small number of studies estimating the prevalence of adult ADHD.

In general, epidemiologic data about adult ADHD have been collected from three different sources in the literature: 1/ family studies; 2/ follow-up studies; and 3/ population-based studies. In family studies, parents of non-ADHD children – who had taken part in case-control type ADHD studies as the control group - were examined for adult ADHD. These studies estimated the prevalence of ADHD to be around 6% among parents of non-ADHD children. The results of these studies cannot be generalised since

they used a strongly selected sample, excluding a genetically predisposed group – parents of children with ADHD (54-60).

1.3.1. Follow-up studies

Follow-up studies are long-term prospective studies, designed for determining the persistence of ADHD among adolescents and adults, by following an index ADHD group of school-age children and a matched control group.

Follow-up studies were usually conducted in 3 steps. The first step was the inclusion, during which the first evaluation of children was carried out. In the majority of the cases children from clinical samples and between the age of 4 and 12 were included (2;4-6;8;61). One study in Sweden examined a birth cohort (3). Inclusion criteria were according to the actual diagnostic system in use at the time of the inclusion. The adolescent follow-up was the second and the young adult follow-up was the third step.

Follow-up studies showed that ADHD persists in 4-66% of the cases into adulthood (2-6;8;61). Such a high variability in the persistence of the disorder into adulthood can be explained, at least in part, by several methodological differences in the respective studies.

First, since the follow-up design requires complex logistical operations, the sample size of these studies was typically rather low. In addition, these studies focused on a clinically referred sample (2;4-6;8;61), except for rare cases where the index group represented a birth cohort (3). Therefore, these studies failed to provide a sample representative of the general population.

Second, at the time of the adult follow-up subjects were between the ages of 19 and 26; thus, follow-up studies did not provide any information about the persistence of ADHD at higher age (2-6;8;61).

Third, for all studies conducted thus far, by the time of the adult follow up the DSM criteria have changed compared to the ones used during the inclusion (2-6;8;61). Furthermore, inclusion criteria were different across studies at baseline and different diagnostic criteria were applied across studies at the follow-up, which makes it difficult to compare the results (2-6;8;61).

Finally, in most of the studies during inclusion and adolescent follow-up parents served as the source of information. However, during the adult follow-up all studies applied self-report, except for the Milwaukee study (2) which used both approaches.

The methodological questions detailed above imply that follow-up studies are difficult to compare and the results of those studies can neither be generalised nor used for estimating prevalence of ADHD in adulthood. However, these studies provided valuable evidence for the validity of the diagnosis in adults, furthermore, they provided initial insight on the poor outcome, functional impairments and psychiatric comorbidity of young adult subjects with ADHD. For example, based on the results of the New York study (5;6;30), during the adult follow-up 33% of the probands vs. 19% of the control subjects had ongoing mental disorders. Antisocial personality disorder (12% vs. 3%, OR:4.0) and non-alcohol substance use disorder (12% vs. 4%, OR:3.8) were the most common comorbid conditions. With regard to education, the New York Study reported that probands completed significantly less years (mean difference: 2.5years, $p<.0001$) of education. Additionally, nearly one-quarter of the probands was dropped out before grade 11 compared with 2% being dropped out from the controls ($p<.001$), and significantly less probands completed Bachelor's degree than did controls (12% vs. 49%, $p<.0001$). These results, as well as the results on significantly lower proportion of professional positions among probands compared with controls (4% vs. 21%, $p<.001$), are in line with most of the other follow-up studies, also reporting on fewer years of education, higher drop-out rate from school and lower occupational ranking.

Table 1-4 summarize the methods and main findings regarding the persistence of ADHD in adults, of follow-up studies.

Table 1. **New York Study (USA) – *Manuzza et al,* 1998**	
Design	3 steps longitudinal, prospective follow-up, based on clinically referred sample. 2 paralel studies for replicating the findings. Adult follow-up took place after 13-19 ys in cohort 1, and 15-21ys in cohort 2.
Sample size (N) – at inclusion	Cohort 1.: **103** (control:100) Cohort 2:. **104** (control:78)
-at follow-up	Cohort 1.: **91** (control:95) Cohort 2.: **85** (control:73)
Age (M) - at inclusion	**6-12 ys**
- at follow-up	Cohort 1.: **25,5** (23-30, SD:1,3); control: 25,6 (23-29, SD:1,6) Cohort 2.: **24,1** (SD: 1,2); control: 23,5 (SD: 1,1)
Gender	**100% male**
Diagnostic procedure *-at inclusion*	Both cohorts: **DSM-II** based clinical diagnosis (Hyperkinetic Reaction of Childhood) Cohort 2. included the Conners Teacher Rating Scale as well: hyperactivity factor > 1,8 (out of 3,0); hyperactivity had to cause significant impairment at home as well.
-at follow-up	Both cohorts: **DSM-III-R** Rater was blind for the inclusion status of the subjects, only assessed adult symptoms when childhood symptoms were reported. *Measure:* self-report, semi-structured interyiew (Schedule for the Assessment of Conduct, Hyperactivity, Anxiety, Mood, and Psychoactive Substances)
Results	**Based on DSM-III-R** Cohort 1.: ADHD persisted in **8%;** in **11%** clinically significant symptoms persisted Cohort 2.: ADHD persisted in **4%**

Table 2. **Göteborg Study (S) – *Rasmussen and Gilberg*, 2001**	
Design	Community, birth cohort based 3 steps prospective, longitudinal follow-up. Sample: from the general population of Göteborg in 1977. Out of the 5114 six years old, 72 % (3448) of the preschoolers (4797) took part in the inclusion process
Sample size (N) –at inclusion	**112 (61** *probands* and **51** *controls)*
- at follow-up	**101** [**55** *proband* (39 ADHD+ DCD[b], 11 ADHD, 5 DCD) and **46** *control]*
Age (M) -at inclusion	**6** (100%)
-at follow-up	**21,9** (21-23, SD: 0,4)
Gender	*Probands*: **42 males** **13 females** *Control:* **20 males** **26 females**
Diagnostic procedure *-at inclusion*	*Screening,* with the Preschool Teacher Questionnaire*,* detailed neurological, psychiatric and neuropsychological examination, free interview with parents. *Diagnosis* based on **DSM-II[b]**
-at follow-up	Based on **DSM-IV**, self-report: *Measure:* CASI (Current ADHD Symptom Interview)
Eredmények	*Probands*: clinically significant symptoms of ADHD persisted: ∑ **49%** (I[c]-15%, HI-44%) *Controls*: clinically significant symptoms of ADHD persisted: ∑ 9% (I-7%, HI-2%)

a-DCD=developmental coordination disorder

b- at early follow-up, based on rediagnosis, cases were in accordance with DSM-III diagnosis

c-I-inattentive symptoms, HI: hyperactivity/impulsivity symptoms

Table 3. **Milwaukee Study (USA)** – *Barkley et al,* **2002**	
Design	3 steps, prospective, longitudinal follow-up, based on clinically referred sample.
Sample size (N) – at inclusion	**158 proband** (81 control)
- at follow-up	**147 proband** (73 controll)
Age (M) - at inclusion	**4-12 ys**
- at follow-up	Probands**: 21,1 ys** (19-25 SD: 1,3) Control: 20,5 ys (SD: 0,6)
Gender	**87% males, 13% females**
Diagnostic procedure *–at inclusion*	**DSM-II, but concordant with DSM-III; Based on parent and teacher rating:** *CPRS-R* Hyperactivity Index (Revised Conners Parent Rating Scale), *WWPARS* (Werry-Weiss-Peters Activity Rating Scale) +2SD difference from the age and gender matched mean +*HSQ (Home Situaton Questionnaire)*
-at follow-up	**DSM-III-R, DRC** [Developmentaly Referenced Criterion –reduced symptom count (4)], parent report also based on **DSM-IV.** *Self-report:*: DSM-III-R based *diagnostic inteview*, *YASR*-t (Young Adult Self-Report for the Child Behavior Checklist-Young) *Parent reporti*: DSM-IV based *diagnostic interview; CPRS-R, WWPARS, CBCL* (Child Behavior Checklist) modified version
Results	Persistence/Incidence (control) based on **self-report**: *DSM-III-R* : Proband: **5%**; Control: 0% - *DRC:* Proband: **12%**; Control: 10% Based on **Parent's report**: *DSM-III-R* : Proband: **46%**; Control: 1% *DRC* : Proband: **66%**; Control: 8% *DSM-IV*: Proband:**58%**; Control: 7%

Table 4. **Montreal Study (CAN) –- *Weiss et al,* 1993**	
Design	3 steps, longitudinal, prospective follow-up, based on clinically referred sample
Sample size (N) – at inclusion	**103**
- at follow-up	**63**
Age (M) - at inclusion	**6-12 ys**
-at follow-up	**25 ys,** (range: 21-33)
Gender[a]	
Diagnostic procedure - *at inclusion*	Persisting, severe hyperactivity and attention problems that cause impairments in both school and at home.
- *at follow-up*	**Based on DSM-III**
Results	42/63 = **66%** showed at least 1 persisiting symptom at follow-up, **36%** showed at least 1 moderately or severly impairing symptom.

[a] Raw data of the original publication was not accessable

1.3.2. Population based studies

Population based studies estimated 1-7.3% prevalence of adult ADHD applying DSM-IV criteria (35;40;54;62-68). Most of these studies were designed for direct estimation of the prevalence of adult ADHD in a given target population such as a community, university students, prisoners or special population of patients. Here, I present only those studies that estimated the prevalence of adult ADHD in community samples or among university/college students, since these studies are methodologically the closest to the topic of this dissertation.

Murphy and Barkley (69) published the first, systematically assessed prevalence data of ADHD on a community based, adult sample (N=720). They included subjects applying for obtaining or renewing their driver's license and used a DSM-IV based symptom list for assessing childhood and ongoing ADHD symptoms. Estimated prevalence rate was 4.7%. ADHD symptoms showed decline with age in this sample, however, being a cross-sectional study this finding has to be interpreted cautiously, as it was noted also by the authors. There was no significant gender effect on the frequency

of current symptoms. ADHD symptoms were negatively correlated to the years of education and socio-economic status. This study addressed for the first time the issue of DSM-IV diagnostic threshold being over-restrictive when applied in adults, based on findings on a community sample. Specifically, these authors suggested to introduce developmentally referenced criterion for the diagnosis of ADHD, by setting the threshold at a symptom count that is endorsed by less than 10% of the age-appropriate population. Reported findings of this study indicated that the actual DSM-IV threshold falls 2.5 to 3 SD above the mean (>99 percentile).

Kooij et al. (62) conducted a community based study estimating the prevalence of adult ADHD, investigating the internal and external validity of the disorder and addressing the issue of whether which symptom threshold is predictive for functional impairment. A random, 5% sample (N=4517) of the population of Nijmegen (n=80315) was approached through GP practices, from which sample, 1815 subjects were included in the study. Raw prevalence estimates were weighted by data of the Central Bureau of Statistics of The Netherlands (based on age and gender), in order to derive prevalance estimates generalisable for the population.

In this study a modified, Dutch version of a DSM-IV based structured interview was employed, including three core symptoms for retrospective childhood assessment as well. Next to assessing ADHD symptoms, self-perceived psychosocial functioning was also evaluated.

During data analysis, diagnosis of adult ADHD was defined in two ways: 1) based on DSM-IV criteria, 2) based on symptom threshold reduced to 4 symptoms compared to the original DSM-IV symptom criterion that requires 6 symptoms to be present from the 9 inattentive and/or 9 hyperactive/impulsive symptoms. This latter criterion was based on detailed analysises of covariance, investigating the relationship between functional impairment and symptom count. Based on the analysis, significantly higher level of self-perceived psychosocial impairment was associated with the presence of 4 or more ADHD symptoms (either inattentive or hyperactive/impulsive), than with the presence of 3 or less ADHD symptoms.

Reported findings showed that employing diagnostic criterion 1, prevalence estimate of ADHD was 1% in this sample; based on criterion 2, prevalence rate increased to 2.5%.

When applying criterion 2, prevalence of ADHD was higher among females [odds ratio (OR) 2.6, 95%CI 1.4-4.7, $p<0.05$]. Regarding age there was no significant association with the prevalence of ADHD either when applying criterion 1 or 2.

Based on the confirmatory factor analysis, authors suggested that the three-factor model (inattention, hyperactivity and impulsivity) of ADHD, previously confirmed in case of children, can be generalised to adults.

Faraone and Biederman (54) published the results of a telephone survey, during which 5000 USA residents older than 18 years were approached. From the approached sample, 1019 subjects agreed on participating, however, only data of 966 included subjects were analysed, due to missing data.

For the assessment of symptoms of ADHD both in childhood and in adulthood, DSM-IV symptom lists were used. For the diagnosis of ADHD at least 6 of the 9 symptoms of inattention and/or hyperactivity/impulsivity had to be reported. Authors defined two diagnostic groups: 1) „narrow"ADHD included those subjects who met the above criterion and indicated the symptom frequency as „often"; 2) „broad" ADHD included those subjects who met the criterion of symptom count, but indicated the symptom frequency as „often" or „sometimes". This latter diagnostic group was defined for establishing a relatively more sensitive diagnostic criteria for screening purposes in the future.

Prevalence estimates were reported as follows: „narrow" ADHD: 2.9%; „broad" ADHD: 16.4%.

Among all subjects the prevalence of previously diagnosed ADHD by a professional, was 4.4%. In both diagnostic groups the prevalence of previously diagnosed ADHD was significantly higher than in the non-ADHD group. Notably, in the non-ADHD group the prevalence of previously diagnosed ADHD cases was 3.5%. This rate dropped to 1.3% when excluding those subjects from the non-ADHD group who reported subthreshold symptom count for childhood ADHD.

The „broad" ADHD diagnosis was more prevalent among males (males: 19.4%, females: 13.4%, $\chi 2=5.7$, $p<0.02$). Concerning age, results showed that the „narrow" ADHD group was significantly younger than the „broad" ADHD group. The prevalence of ADHD was the highest in North-East and North-Middle states. ADHD with both diagnostic approach was more prevalent in cities (>15000 citizens) than in villages and

rural areas. The significance of this latter association disappeared in case of the „broad" ADHD when controlled for age and gender. Results also showed that unemployment was 2.6 times higher in the „narrow" ADHD group compared with the non-ADHD group.

Almeida Montes et al (35) reported on prevalence estimates among 161 adult outpatients with nonpsychotic psychiatric illnesses and 149 healthy participants who came to the mental health outpatient service for other reasons than psychiatric consultation. This latter group did not include those individuals who had prior history of psychiatric service assistance or psychiatric treatment, had first degree relatives with ADHD or any other psychiatric disease, had any other medical conditions. Thus, as it was discussed earlier regarding family studies, this study excluded a genetically predisposed group which might result in underrepresentation of subjects with ADHD.

During the assessment of ADHD the M.I.N.I. Structured Interview (70) was used, which is a DSM-IV based diagnostic tool. The authors applied several further clinical rating scales for evaluating other psychiatric conditions than ADHD.

Prevalence of ADHD was significantly higher, 16.8% in the psychiatric outpatient population, compared with the non-clinical population, where prevalence was 5.37% (χ^2 =8.680, df=1, p=.003). While in the psychiatric outpatient population there was a significant difference between the prevalence rates by gender (males:8.5%, females: 21.6%, χ^2= 4.59, df=1, p=.032), this difference was not significant in the non-clinical population (males: 4.1%, females: 7.1%, χ^2= 0.494, df=1, p=.482). With regard to psychiatric comorbidity, in the psychatric outpatient population affective and anxiety disorders were the most frequent comorbid conditions. Subjects diagnosed with ADHD from the non-clinical population showed more severe anxiety and affective symptoms than did those from this group without ADHD.

Gadow et al (71) reported on data of a large sample of adults (n=900), representative to the general population, as part of publications of the standardization process and the validity of a DSM-IV referenced rating scale (Adult Self-Report Inventory-4 – ASRI-4) assessing several psyhiatric conditions, and publication of the validity of oppositional defiant disorder as a behavioral syndrome in adults. Based on the descriptive results provided, there were 60 subjects out of 900, diagnosed with ADHD with this diagnostic tool.

There are four studies investigating the prevalence of ADHD, or ADHD symptoms among college/university students. Weyandt et al (67) reported on the prevalence of ADHD symptoms among college students (N=770), using the WURS (45) for assessing childhood symptoms and the ADHD Rating Scale (ARS) (72) for assessing adult symptoms. Results showed that 7% and 8.7% of the subjects reported significant symptoms (1.5 SD above the mean, 93th percentile) on the ARS and the WURS, respectively and 2.5% of the subjects fell 1.5 SD above the mean on both rating scales, indicating significant ADHD symptoms in both childhood and adulthood. When criteria was set at a more restrictive level (2 SD above the mean, 98th percentile) there was 0.5% of the subjects, who reported significant symptoms on both rating scales and 4.7% who reported significant symptoms on 12 items of the ARS that corresponded to symptoms determined in DSM-IV.

Heiligenstein et al (64) analysed data of 448 university students. Diagnosis of adult ADHD was based on the ARS (72). When determining diagnostic criteria the authors used two approaches. First, DSM-IV thresholds were applied and second, the previously described developmentally referenced criterion was used. Threshold for the latter criterion was created based on the 93th percentile (1.5 SD above the mean), that corresponded to 4 symptoms to be present out of 9 symptoms of inattention and/or hyperactivity, based on the analysis of the authors. Prevalence rate was 4% based on DSM-IV criteria and 11% based on the modified criteria. There was no association between ADHD symptoms and gender, ethnicity and educational level in either case of diagnostic approach. However, there was a negative correlation between hyperactive symptoms and age.

DuPaul et al (63) made an effort to increase the precision of prevalence estimates of ADHD among college students by means of significantly enlarging the sample size and extend the survey to more countries. Overall, 1209 students from 3 countries (USA, Italy, New-Zeland) took part in this study. A self-report DSM-IV questionnaire, the YARS (Young Adult Rating Scale) (63) was applied to assess ADHD symptoms. Similar to previously introduced studies, these authors applied modified threshold (3 symptoms to be present in this case) for the diagnosis of ADHD, next to DSM-IV threshold, although onset criterion, functional impairment and retrospective data from childhood were not captured as noted also by the authors. Based on DSM-IV

threshold, prevalence estimates yielded as follows: USA: 2.9% in males, 3.9% in females; New-Zeland 8.1% in males, 1.7% in females; Italy: 7.4% in males and 0% in females. Modified diagnostic criteria elevated the prevalence estimates so dramatically, between 26 and 43% (latter in females from Italy!) that these estimates cannot be interpreted along practical considerations.

Norvilitis et al (73) published recently the results of their study, investigating the frequency of ADHD symptoms among college students from the USA (n=283) and China (n=343). This report also examined the validity and reliability of the Chinese version of WURS (assessing retrospective data on ADHD symptoms in childhood) and the Current Symptoms Scale (CSS – assessing current ADHD symptoms in adults) (74). Overall, on both WURS and CSS symptom counts, 2.3% of the American and 1.2% of Chinese participants were above the threshold ($\chi 2$ [589] = 1.14, $p > .05$), while 1.7% of the American and 2.7% of Chinese participants were above the threshold on both the WURS and CSS overall scores ($\chi 2$ [568] = .357, $p > .05$). Additionally, results showed that Chinese participants scored lower on childhood symptoms and higher on adult symptoms compared with American participants and in both samples more ADHD symptoms were correlated with higher level of depression and lower self-esteem.

Two studies, being parts of large-scale epidemiological surveys - the National Comorbidity Survey (75) and the WHO World Mental Health surveys (76) used indirect estimation in order to asses the prevalence of adult ADHD in the general population. The first of these studies (65) examined an US sample, whereas the second one (66) estimated cross-national prevalence in 10 countries. Both studies used the same methodology, specifically they interviewed a large probability sample of subjects (N=3199 in the US study and N=11422 in the cross-national study) between the age of 18 and 44. Childhood ADHD was retrospectively assessed based on DSM-IV criteria and there was a single question targeting whether the subject had still ongoing problems with ADHD symptoms. Among those subjects who answered ’yes’ to this latter question (~70%), a probability subsample of 100 individuals, and a probability subsample of 50 non-ADHD individuals, were included in a face-to-face detailed diagnostic interview, using the Adult ADHD Self-Report Scale (77), a DSM-IV based questionnaire. We note that despite applying the same general approach in both studies, the first study estimated a 4.4% prevalence, whereas the second one estimated 5.2%

prevalence of adult ADHD in the same US sample (65;66). Based on the authors' comment, this discrepancy between the two studies is attributable to the fact that certain predictors for the prevalence estimation that were used in the first (i.e., US) study were not available in the second (multinational) study.

In the second study, the prevalence estimates of adult ADHD across samples showed a substantial variation; they were between 1.2% and 7.3%, with an estimated general cross-national prevalence of 3.4% (66). Prevalence estimate in France yielded significantly higher than the average cross-national prevalence, while estimates in Colombia, Lebanon, Mexico and Spain yielded significantly lower than the average. Prevalence estimates from the cross-national study are shown in Table 5.

Table 5.
Prevalence rates found in the multinational WHO study (66)

Country	**N**	**Prevalence estimates % (standard error)**
Belgium	486	4.1 (1.5)
Colombia	1731	1.9 (0.5)
France	727	7.3 (1.8)
Germany	621	3.1 (0.8)
Italy	853	2.8 (0.6)
Lebanon	595	1.8 (0.7)
Mexico	1736	1.9 (0.4)
Netherlands	516	5.0 (1.6)
Spain	960	1.2 (0.6)
USA	3197	5.2 (0.6)
Total	11422	3.4 (0.4)

Both studies found that ADHD was more common in males and in those with less years of education, furthermore ADHD was associated with higher number of divorces and higher rates of unemployment. Regarding psychiatric comorbidity, both studies reported on significantly more frequent comorbid disorders in the past 12 months (mood, anxiety, substance use and impulse control disorders) among the ADHD

group compared with the non-ADHD group (65;66). These reported comorbidity data are briefly summarized in Table 6.

Table 6.
Comorbidity of adult ADHD with other DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R) (N=3199) and in the multinational WHO study (N=11422)

	NCS-R[1]		**Multinational study**	
Classes of comorbid disorders	**%**	**OR[2]**	**%**	**OR[2]**
Any mood disorder	29.9	3.5*	24.8	3.9*
Any anxiety disorder	47.0	3.4*	38.1	4.0*
Any substance use disorder	14.7	2.8*	11.1	4.0*
Impulse control disorders[3]	35.0	5.6*	NR[4]	NR[4]

1: These figures are based on Spencer TJ (2008)

2:OR= Odds Ratio

3: Impulse control disorders included: antisocial personality disorder, oppositional defiant disorder, conduct disorder, intermittent explosive disorder, pathological gambling and bulimia

4: NR= non reported

**p≤.05, compared with non ADHD group*

Additionally, authors of both studies emphasized that the reported prevalence rates might underestimate the true occurrence of this disorder in adulthood, due to the applied methodological factors (only self-report was used, indirect estimation methods) and also due to the lack of standard method for the validation of adult ADHD. These authors, similar to others published in this field, found the DSM-IV diagnostic criteria of ADHD over-restrictive when applied in adults (65;66).

2. Objectives

As it was discussed earlier, ADHD is a remarkably disabling disorder, carrying an elevated risk for comorbid psychiatric conditions and maladaptive personality development as well. Furthermore, the significant negative impact of this disorder affects not only the individual's life but the society as well. Taking into consideration these broadly impairing effects, and the fact that effective treatment tools exist in the management of ADHD both in childhood and in adulthood (26;27), identifying and diagnosing ADHD is crucial.

To date, in Hungary, no epidemiologic survey has been conducted for the estimation of the prevalence of adult ADHD. Furthermore, not only public, but professional awareness is also lacking about this disorder. Although ADHD in childhood is well known and treated condition in Hungary, the treatment of those individuals diagnosed with ADHD in childhood and continuously showing impairing symptoms in adulthood is not solved yet. In addition, outpatient services dedicated for the treatment and diagnosis of adult ADHD are completely missing.

Hence, the objectives of this dissertation were the following:

1) To estimate the prevalence of adult ADHD for the first time, in a large (N=3529) Hungarian community sample, with the inclusion of 17 GP practices in Budapest.

2) To investigate how do different diagnostic criteria affect the prevalence estimates of adult ADHD, in the same Hungarian GP population.

3) To pool the prevalence estimates published in the literature and to identify correlates of the prevalence of adult ADHD by employing a meta-analytic approach.

4) To examine whether those correlates have a similar effect on the first hungarian prevalence estimates.

5) The fifth objective of this dissertation was rather speculative. Specifically, it implicated that Hungary is a country where public and professional awareness were both missing regarding adult ADHD. This means that case identification would not be biased by professional „attention preference", or public „overcommunication of the disorder". People of Hungary practically do not know and the majority of people have not even heard about this disorder. I assumed that if the results of our estimation will be comparable to those prevalence estimates reported in the literature, it might provide, although indirectly, but additional support for the validity of the diagnosis.

3. Methods

In general, there are two issues that have to be discussed before the detailed description of the methodology of the presented two studies.

First, due to logistic and practical reasons the chronology of the two studies was as follows: Since the epidemiologic study needed complex logistic operations and a year time to conduct, we applied sample size estimation based on the prevalence estimates published in the literature in order to finalize the protocol and start the screening. In the meantime we managed to finish our meta-analysis that resulted in a slightly different pooled prevalence estimate and also defined certain correlates of the prevalence of adult ADHD. Based on this pooled prevalence estimate and the preliminary results of the epidemiologic study we re-run the sample size estimation (see detailed description below) for the refinement of the sample size needed for a more accurate prevalence estimation in our study sample.

For a better flow and readability I will describe throughout this work the methods and results of the meta-analysis first, and the methods and results of the epidemiologic study second, while in the discussion I will discuss our findings by relevant topics.

Second, with regard to the methodology of epidemiologic studies in general, we must emphasize again, that one of the crucial points is case identification. However, as it was discussed earlier, there are no validated diagnostic criteria and professional consensus on the diagnosis of ADHD in adults. Furthermore, the studies estimating the prevalence of adult ADHD differed greatly in the diagnostic tools and diagnostic criteria applied, as well as general setting and sample. When starting our work we faced two problems: 1) based on what type of published data should we carry out the meta-analysis in order to be inclusive enough but not to result in extreme heterogeneity? and 2) how to design our epidemiologic study, which setting and which diagnostic criteria/tools should be applied?

We found that DSM-IV diagnostic criteria was the common point across majority of the previous studies. Thus, we based our meta-analysis on studies that provided prevalence estimates based on DSM-IV and in our epidemiologic study the „baseline" or „reference" diagnosis was also based on DSM-IV criteria.

3.1. Methods of the meta-regression analysis

3.1.1. Study selection

We used Medline, Psychlit and Embase databases, searching for publications dealing with the epidemiology of adult ADHD. Only publications in English were considered. As a first step, we created 4 basic databases with the following keywords: „adult", „adhd", „epidemiology", and „prevalence". Second, we connected two databases („adult", „adhd") with a logical „AND" operation; this resulted in a new database with only those publications that were parts of both „adult" and „adhd" databases in the first step. The other two databases: „epidemiology" and „prevalence" were connected with the „OR" operation, thus in this new database all publications were included that were originally in „epidemiology" and „prevalence". During the last step, the two new databases were connected with „AND" operation.

In addtion to the above search procedure, we used the reference list of the identified publications to find further relevant articles. After excluding follow-up and family studies – that do not provide prevalence data of adult ADHD -, and those studies that were dealing with the prevalence of ADHD in special groups (patients with panic- or bipolar disorder, drug addicts, obese patients, prisoners), we found 12 population-based studies remaining:

- 1 study estimated the *cumulative incidence* of ADHD at the age of 19 based on *retrospective analysis*: Barbaresi et al*,* 2004 (78)
- 1 study estimated the prevalence of adult ADHD among *licensed drivers:* Murphy and Barkley, 1996 (69)
- 3 studies estimated the prevalence of ADHD among *university students*: Weyandt et al*,* 1995 (67); DuPaul et al*,* 2001 (63); Heiligenstein et al, 1998 (64)
- 1 study estimated the prevalence of ADHD among nonclinical subjects from an outpatient psychiatric service: Almeida Montes et al (2007) (35)
- 4 studies provided a *community based* estimate:
- Oppositional Defiant Disorder (ODD), ADHD, versus ODD+ADHD in clinic and community adults by Gadow et al. 2007 (71); – Cross-national Survey by

Fayyad et al, 2007 (66); – National Comorbidity Survey Replication (NCS-R) by Kessler et al, 2006 (65); - Mexican National Comorbidity Survey (M-NCS) by Medina-Mora et al, 2005 (68); – Telephone survey by Faraone and Biederman, 2005 (54); – Nijmegen Health Area Study 2 (NHA-2) by Kooij et al, 2005 (62)

In our meta-regression analyses, six studies were not included. Three of these studies – the studies of Kessler et al (65), Medina-Mora et al (68) and Fayyad et al (66) - were not included because they did not provide raw data for the prevalance and demographic variables necessary for the computations. The study of Barbaresi et al, (78) was not included since it deals only with the cumulative incidence of ADHD between the ages of 5 and 19, and accordingly, it provides information about ADHD in adolescents rather than in adults. The study of Weyandt et al (67) was not included in our analysis since it measured only the prevalence of attention deficit *symptoms* and not the prevalence of adult ADHD. Finally, we did not include in the analysis the study of Gadow et al (71), because these authors did not use DSM-IV criteria (40) for the diagnoses of adult ADHD. The modified diagnostic criteria applied by Gadow et al (71) did not include age of onset and functional impairment criteria, and applied a threshold of 5 instead of 6 symptoms. As will be shown later, lowering the diagnostic threshold concerning symptom counts has a dramatic effect on prevalence estimates; inclusion of data based on a lower symptom threshold would therefore had introduced a substantial heterogeneity in the meta-analysis.

3.1.2. Variables

For the purpose of the meta-analysis we extracted the following domains/variables from the articles that were finally included:

- descriptive data on the publication - *date of publication, country, number of arms*
- descriptive data on the target population - *sample size, mean age, age range, standard deviation for age range, gender composition (proportion of males in the sample)*
- diagnostic tool for adult ADHD – *self-report, structured interview*
- results - *prevalence rate according to DSM-IV criteria* (total and subtypes if provided), *prevalence rate according to alternative criteria*, if available (total and subtypes, if given).

3.1.3. Statistical analysis

The Statistical Analysis System for Windows (version 9.1; SAS Institute, Cary, NC) was used for statistical analyses. A mixed-effect (with fixed and random effects) meta-regression - a meta-analytic technique of multivariate linear regression across studies - was applied to estimate the prevalence of ADHD across various study samples and in order to evaluate the impact of potential demographic variables of interest including age and gender on the prevalence estimates. The meta-regression analysis that we adopted in this investigation was based on van Houwelingen et al's general linear mixed-model technique based on the approximate likelihood approach (79). In particular, the log-odds of the observed prevalence in each study was regressed on an intercept and basic study-level demographic covariates that included average age and gender composition from each of the individual studies. Interaction between the two covariates (age, gender composition) was also included in the model. In addition, a random-effect intercept-term representing systematic between-study variation (heterogeneity) was also incorporated in the meta-regression model. A common weighted prevalence estimate for ADHD was calculated as a deSimonian and Laird

estimator based on the random effects component of the mixed model that incorporated both fixed and random effects (80).

3.2. Methods of the first Hungarian study estimating the prevalence of adult ADHD on a community sample

This investigation was part of a larger study examining the epidemiology, neuropsychology, genetic background, psychopathology and clinical features of adult ADHD. The parent study was a multiphase, multicenter study including the Semmelweis University, Department of Psychiatry and Psychotherapy, and 17 general practitioners (GP) in Budapest.

3.2.1. Sample and data collection

Between June 2006 and June 2007, 3529 patients of 17 GP practices entered the epidemiological study in the area of Budapest, Hungary. Data collection took place in the participating GP practices. Subjects between 18 and 60 years from both genders without major neurological disorder in their clinical history were included in the study. During the *screening phase,* consecutively arriving patients entered in the study every office day of the GPs. The assistant distributed the ADHD screener to the subjects. Positively screened subjects (n=279) were asked by the GP to further participate in the *interview phase* of the study. From this sample of positively screened subjects 29.4% (n=82) refused participation in the interview phase and 12.9% (n=36) failed to show up.

In the *interview phase,* positively screened subjects enrolled for this phase (n=161) participated in a clinical interview and filled out a self-report questionnaire in order to confirm the diagnosis of adult ADHD. During the clinical interview, beside demographic data and diagnosis of adult ADHD, other potential comorbid psychiatric disorders and neuropsychological functioning were assessed, and samples for genetic studies were gathered. These latter data will be reported in upcoming publications.

GPs and assistants underwent a training on the study protocol and basic information on adult ADHD. The clinical interviews were conducted by one of the three trained interviewers, two psychologists and one psychiatrist resident. Inter-rater reliability of the clinical diagnosis of adult ADHD was assessed, based on the DSM-IV

symptom list and free clinical interview conducted in the study. Inter-rater reliability among the three raters with regard to the assessment of the DSM-IV clinical symptoms, estimated by intra-class correlation coefficient (ICC), was 0.85. Interrater agreement regarding the clinical impression of ADHD, as measured by coefficient kappa, exceeded 0.90.

All participants in the interview phase received a 2000 HUF gift card as a compensation for providing genetic sample, according to the pertinent regulations in Hungary.

This investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the local ethics committee and all included subjects provided written informed consent.

3.2.2. Estimation of the sample size

Estimation of the sample size for the study was based on the binomial model. The input parameters for the estimation were the Type I error probability (alpha=0.05), the confidence coefficient (95% confidence), the estimated baseline proportion of the prevalence of ADHD in the study population, and the required precision of the estimate (half the width of the 95% confidence interval). In particular, based on prior reports from the literature for the baseline proportion the value of 2.5% posited; for the precision of the estimate, a value of 0.5% was adopted for the sample size computations (81-83)]. Results of these computations indicated that 3534 subjects would be sufficient to yield an estimate of prevalence with the required precision.

3.2.3. Measures

Adult ADHD Self-Report Scale (ASRS): ASRS is an 18-item self-report scale, based on the symptom-list of DSM-IV, developed by the Workgroup on Adult ADHD in conjunction with the World Health Organization (WHO) (77). Symptom frequency is measured on a 5-point Likert-scale. In the screening phase of the study the 6-question, screener version of ASRS was applied. This short version of ASRS has good sensitivity and specificity as well as predictive value for the diagnosis of adult ADHD, as reported

previously in the literature (77). While during the interview phase subjects completed the full ASRS, this dataset was not included in the present analysis.

DSM-IV symptom list: A structured interview has been developed by the authors, using the symptom list of ADHD in DSM-IV (Hungarian version (84)), including functional impairment and onset criteria (i.e., whether some of the symptoms had caused problems before the age of seven) as well. The interview comprised two sections. The first section assessed the presence of ADHD in childhood and included 20 items: 18 symptoms, functional impairment and onset. The second section assessed the presence of adult ADHD based on the same items as in the first section (with the exclusion of onset, which has already been collected in the 1st section); functional impairment (yes/no) was established based on whether the symptoms were present and caused problems during the past half a year.

Free clinical interview: During the free clinical interview the interviewer had 20-30 minutes in order to collect relevant background information for supporting the validity of the clinical diagnosis. The type of information needed to be gathered was the same for all the participants, but the interview was conducted in an open-ended fashion while the interviewers were making detailed notes. The following issues had to be addressed: complications during pregnancy and delivery; developmental differences; family background (relationship with parents, siblings, brief family history); preschool nursing (problems with the other children, problems with the preschool teachers, adjustment problems); school years (studies, behavior, relationship with students/teachers); jobs (conflicts with colleagues/supervisors, frequent job and/or workplace changes); relationships; and whether the participant was satisfied with his/her life, if not what would s/he change?

Demographic and clinical characteristics: The following items were included in the assessment of demographic and clinical characteristics: age, gender, years of education, type of education, marital status, actual reason for visiting the GP (administrative or somatic), psychiatric and somatic history, family history, medications taken on a regular basis, smoking status, handedness.

3.2.4. Diagnosis of adult ADHD

Based on the documentation of the interview and the DSM-IV diagnostic criteria the interviewer team decided whether the participant fulfilled the criteria for the clinical diagnosis of adult ADHD. However, similar to other adult ADHD prevalence studies (54;62;64), alternative groups were created next to DSM-IV diagnosis:

1. *'ADHD_DSM-IV' diagnostic group:* based on full DSM-IV criteria for both childhood and adult ADHD (combined, inattentive or hyperactive/impulsive type) with supporting background information based on the clinical interview.
2. *'ADHD_No-onset' group:* based on DSM-IV criteria for both childhood and adult ADHD (combined, inattentive or hyperactive/impulsive type), excluding onset criterion.
3. *'ADHD_full/Sx' group:* based on DSM-IV symptom criterion only (6 symptoms had to be present out of the 9 symptoms of either inattention or hyperactivity/impulsivity, or both) for both childhood and adult ADHD.
4. *'ADHD_reduced/Sx' group:* based on a reduced number of symptoms present from DSM-IV symptoms (4 out of 9 symptoms of either inattention or hyperactivity/impulsivity, or both) in adulthood, while in childhood original DSM-IV symptom criterion had to be present.

3.2.5. Statistical Analysis

The Statistical Analysis System for Windows (version 9.1; SAS Institute, Cary, NC) was used for statistical analyses. All statistical analyses used the alpha error level of 0.05 (two-sided) and 95% confidence intervals. Demographic and basic background characteristics were summarized by descriptive statistics, including frequency tables for discrete variables and n, mean, SD and minimum and maximum for continuous variables. For the purpose of inferential statistical analyses, the group comparisons were based on the General Linear Model (GLM) approach. In the GLM model, each demographic and descriptive variable of interest served as a dependent variable (in separate analyses). The grouping variable (e.g., ADHD yes vs, no) served as an

independent variable in the GLM analysis. Group differences in terms of categorical variables (e.g., gender distribution) were investigated by Chi-square analysis.

Estimation of prevalence from the study sample was based on the binomial model using the proportion of the subjects who screened positive on the ADHD screener test. For the estimation of 95% confidence interval around the sample proportion of positive cases, the sample estimate of the standard error was adopted. For the computation of the standard error, the following formula was applied:

SEp = sqrt[p * (1 - p) / n], where n, p and SEp denote the sample size, the estimated proportion of cases (subjects with ADHD), and the standard error of the estimate, respectively.

Since screening tests are not ideal (i.e., are less than 100% accurate) in most practical applications, the estimated positive fraction of the sample from such tests cannot be directly applied for determining the true population prevalence of a disease. In order to determine the true population prevalence, one has to take into consideration the established specificity and sensitivity of the test under consideration. Adjusting for the screening test's specificity and sensitivity, Gart and Buck provided an estimate of the true population prevalence using the following formula (85).

PREVp = (POS + Sp -1)/(Se + Sp -1), where PREVp, POS, Sp and Se denote, respectively, the true population prevalence, the proportion of positive cases in the sample, and the specificity and the sensitivity of the screening test. For the specificity and sensitivity of the ASRS screener that we used in our study, we adopted published values from the pertinent literature based on the investigation of large samples of subjects (77).

We note that in addition to the estimate of the overall prevalence of adult ADHD in the entire study population, separate estimates were derived for the males and females, respectively. The rationale for a separate estimation by gender was that the true positive fraction of population showed a significant difference between males and females (see Results later for details).

3.2.6. Variables

Principal variables of interest for this investigation included the following:

- screening outcome (positive/negative)

- total score and three subscale scores of ASRS, including inattention, hyperactivity and impulsivity
- Indices of functioning based on the interview (functional impairment present due to ADHD symptoms)
- Onset criteria based on the interview (whether some of the ADHD symptoms were present and caused problems before the age of seven)
- DSM-IV based clinical diagnosis and alternative diagnostic groups (detailed above).

4. Results

4.1. Results of the meta-regression analysis

4.1.1. Basic descriptive information about the studies included in the meta-analysis

Sample: In all articles that we included in the analysis we found that, while the sample size was large (typically several hundreds of subjects), the authors collected samples of convenience, which do not assure representativeness. Accordingly, the raw estimates of prevalence from these studies cannot be extended to the general population. We note that in the study of Faraone and Biederman (54) raw prevalence estimates were weighted by the US Census data (based on age, race, education, geographic region and number of telephone lines within the household) in order to derive prevalance estimates generalisable for the population. However, the final derived prevalence estimates remain questionable in light of the high refusal rate (approximately 79.6%) in the target population that was used to derive the prevalence estimates in the sampling phase of the study. In the study of DuPaul et al (63), in addition to the problem with representativeness, there were remarkable differences across the 3 subsamples concerning sample size, gender, and the age range of the participants (see Tables 7. and 8.).

Age: In most of the studies, the sample's mean age was low compared to the mean age of a typical adult population. Specifically, while the mean ages were between 19.4 and

44.9 years based on all samples taken together (mean age, weighted by the number of participants in each study, was 34 years), for the majority of samples the mean age ranged between 19.4 and 28.5 years. Only one study (Kooij et al,(62)) had a mean age of 44.9 years whereas two studies had a mean age of around 35 years (Faraone and Biederman, (54); Murphy and Barkley, (69)). (Of these two studies, the study of Faraone and Biederman (54) provided estimates for mean age based on weighting using the US Census data; see more details in Table 7.).

Gender: With the exception of one study sample (the USA arm of the study of DuPaul et al (63)), the gender proportions were neither balanced nor representative for the target population. There were extreme differences in the male-female ratio across the subject groups of the study of DuPaul et al (63), with a substantial departure from the population gender distribution in two arms of this study, possibly as a result of the already mentioned convenience sampling. (Table 7.).

Table 7. Demographic data of studies included in meta-regression analysis

Study	*Sample size*	*Age (years)* *Mean (SD)* *Age range*	*Gender proportions* *Male/female (%)*
Murphy and Barkley (1996)	720	35 (13.2) 17-84	60/40
Heiligenstein et al (1998)	448	20.6 (4) 17- 46	56/44
Du Paul et al (2001) [a]	1209		
Italy	197	[b]21.6 (3) 18-35	13.7/86.3 [b]
New-Zeland	213	19.4 (4) 17-51	17.4/82.6
USA	799	21.3 (4.9) 17-49	50.9/49.1
Kooij et al (2005)	1815	44.9[c] 18-75	44.7/55.3
Faraone and Biederman (2005)	966	35.9[d]	48/52
Almeida Montes et al (2007)	149	28.5	32.9/67.1

a- data available separately by subsample (country) in the original publication

b-calculated by current authors based on the given data (number of females and males in all groups)

c- calculated by current authors from the given proportion of age range groups and N

d- from US Census Data that was referred in the original article

Table 8. Descriptive data of population based studies estimating the prevalence of ADHD

	Design	*Diagnostic procedure*
Murphy and Barkley (1996)	- 1 stage sampling - community based study - non-representative, sample of convenience	DSM-IV symptom list self report
Heiligenstein et al (1998)	- 1 stage sampling - college students - non-representative, sample of convenience	DSM-IV symptom list self-report no data from childhood
Du Paul et al (2001)	- 1 stage sampling - 3 arms - university students - non-representative, sample of convenience	DSM-IV symptom list self-report no data from childhood
Kooij et al (2005)	- 1 stage sampling - community based study in GP practices - non-representative, probability sample	DSM-IV Modified Dutch Version of DSM-IV ADHD Rating Scale self report and structured interview
Faraone and Biederman (2005)	-1 stage sampling - community based telephone survey - non representative, probability sample	DSM-IV symptom list self report
Almeida Montes et al (2007)	-1 stage sampling - nonclinical population from a psychiatric outpatient service - non representative, sample of convenience	DSM-IV M.I.N.I. Structured Interview

Diagnosing adult ADHD: The studies included in our meta-analysis applied different methodology and design with regard to sampling and diagnosing of adults with ADHD (see more details in Table 8.).

All studies employed DSM-IV (40) diagnostic criteria despite the fact that all – except for Faraone and Biederman (54) and Almeida Montes et al (35)- questioned the validity of DSM-IV criteria of ADHD (40), when applied to adults. In terms of association between symptoms that underlie the DSM-IV diagnosis of adult ADHD and the functional impairment (used as an external validator of the disorder), Kooij et al (62) found the strongest association from 4 symptoms being present (as opposed to the threshold of six symptoms according to the DSM-IV diagnostic system). DuPaul et al (63) and Heiligenstein et al (64) applied alternative diagnostic criteria with a lower threshold, beside the original DSM-IV criteria (40). While Murphy and Barkley (69) used only DSM-IV criteria in their study, they suggested the possibility of modifying the DSM-IV diagnostic criteria of adult ADHD in the future.

Faraone and Biederman (54) considered two types of diagnoses for adult ADHD: a „broad" diagnosis that serves for screening purposes, and follows the DSM-IV criteria but being more inclusive concerning symptom severity, as well as a „narrow" diagnosis that is based on DSM-IV criteria.

Table 9. Results of the population based studies estimating the prevalence of adult ADHD

	Prevalence-DSM-IV (%)[a]				*Prevalence-other(%)*[b]			
	[c]*Total*	[c]*I*	*HI*	*Comb*	[c]*Total*	[c]*I*	*HI*	*Comb*
Murphy and Barkley (1996)	**4.7**	1.3	2.5	0.9	No such data available			
Heiligenstein et al (1998)	**4**	[d]2.24	0.88	0.88	**11**	[d]3.74	3.96	3.30
					Reduced number of symptoms required (4)			
Du Paul et al (2001)								
Italy	**1.01**	[d]0.51	0.51	0	**42.31**	[d]8.82	23.42	98.68
New-Zeland	**2.81**	[d]0.47	2.34	0	**36.06**	[d]9.50	17.08	9.48
USA	**3.39**	[d]0.75	2.15	0.5	**26.91**	[d]4.97	13.90	7.15
					Reduced number of symptoms required (3)			
Kooij et al (2005)	**1**	0.2	0.5	0.3	**2.5**	0.3	1.2	1.0
					Reduced number of symptoms required (4)			
Faraone and Biederman (2005)	**2.9**	0.7	1.1	1.1	**16.4**	5.8	3.7	6.9
					„broad" ADHD[e]			
Almeida Montes et al (2007)	**5.37**				No such data available			

a- Prevalence- DSM-IV (%) = % prevalence of ADHD in the sample defined by DSM-IV criteria

b- Prevalence- other (%) = % prevalence of ADHD in the sample defined by criteria other than DSM-IV

c –Total: All subtypes of ADHD pooled, I:Inattentive subtype, HI: hyperactive-impulsive subtype, Comb: combined subtype

d-calculated by current authors based on the given data from the original article

e- referred as screening diagnosis in the original article

4.1.2. Estimated prevalence and correlates of adult ADHD

As described in the Methods, mixed-effect meta-regression analysis was applied to estimate the prevalence across samples and to investigate prevalence as a function of gender composition and mean age in the respective samples. Results of the meta-regression analysis indicated that the pooled prevalence of ADHD across samples was 2.5% (95% CI: 2.1-3.1; t=42.3, p<0.0001) (Figure 1.).

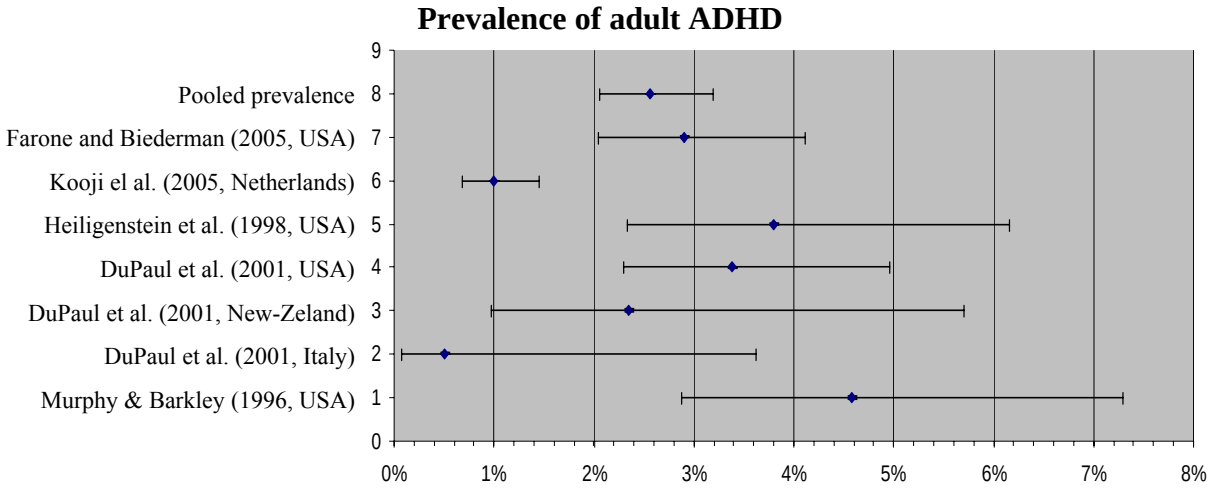
Adopting the likelihood approach as recommended by Hardy and Thompson (86) and van Houwelingen (79), heterogeneity among studies included in the meta-analysis was tested by the likelihood ratio statistic, by comparing the maximum log-likelihood (LL) of the random-effect with that of the fixed-effect model. Our results showed that the random and fixed-models yielded a maximum LL value of -9.9 and -42.5, respectively. This indicates a statistically significant heterogeneity across studies (Chi-square= 65.2, df=1, p<0.0001), which (as shown by subsequent analyses) was due, at least in part, to principal demographic variables that we examined in our study.

In particular, our results showed that the prevalence of ADHD was significantly related to the gender composition in the sample (t=4.34, p=0.012, standardized beta for log-odds of observed prevalence: 15.19×10^{-2}) and to the mean age (t=3.03, p=0.039, standardized beta for log-odds of observed prevalence: 20.98×10^{-2}). Furthermore, the interaction between the two covariates also reached statistical significance (t=.-3.42, p=0.027, standardized beta for log-odds of observed prevalence: 0.50×10^{-2}). The association between the proportion of subjects with ADHD and gender composition and mean age is shown on Figures 2A and 2B, respectively. Due to the statistically significant interaction reported above, for illustration purpose the association of prevalence with gender composition is displayed at various ages (20, 30, 40 years) on Figure 2A. As shown by the figure, for younger age groups the prevalence increases, whereas for the older age group prevalence decreases with higher proportion of males in the sample. Analogously, on Figure 2B for illustration purpose the association of prevalence with mean age was broken down by male percentage of the sample (one-third, one-half, two-thirds). As demonstrated by the figure, the prevalence decreases with age when males are represented at 50% or more in the sample, whereas the

prevalence increases with age when females are predominantly represented in the sample (male percentage=33.3%).

We note that the above results are based on prevalence data that relied on DSM-IV diagnostic criteria. Individual studies included in our meta-analysis used alternative diagnostic criteria as well, but these alternative criteria varied across studies that precludes a meaningful pooling of the results across studies. Indeed, as Table 3. shows, these alternative thresholds lead to substantial variation in the results (prevalence between 2.5% and 42.3%), reflecting the heterogeneity of the alternative diagnostic approaches in the individual studies.

Figure 1.



Prevalence estimates (95% Confidence Interval) of adult ADHD in individual investigations and pooled prevalence estimated across studies using meta-regression analysis.

Figure 2A

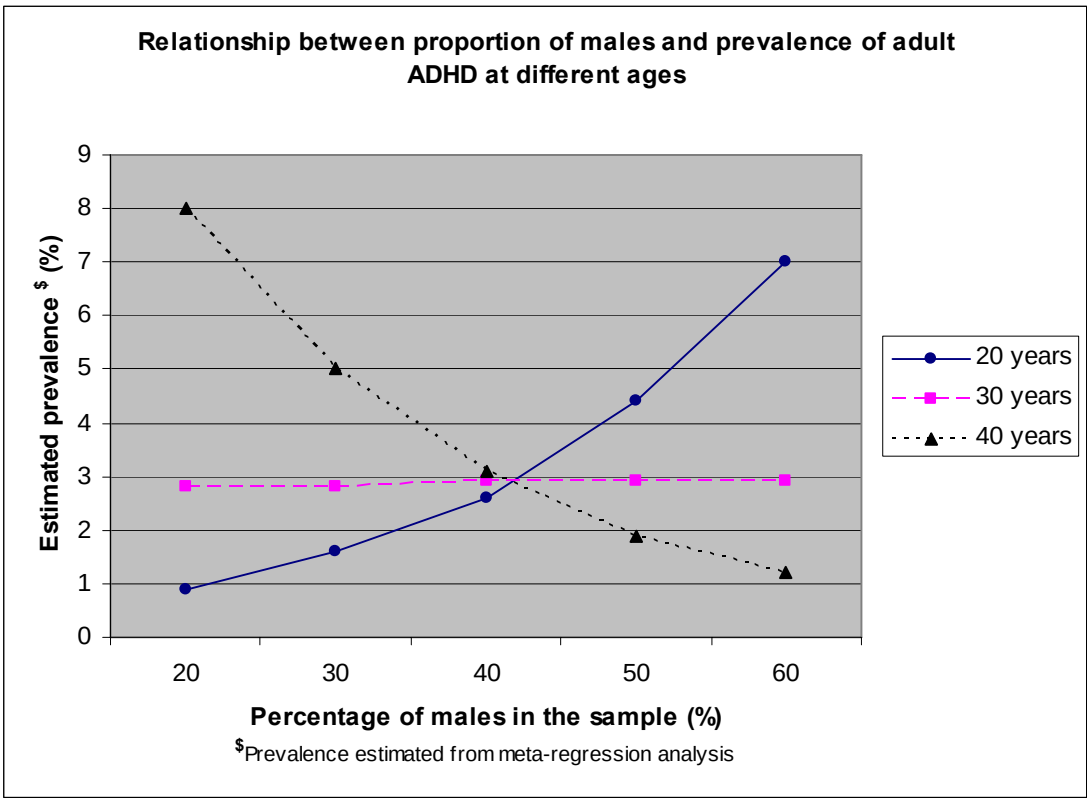
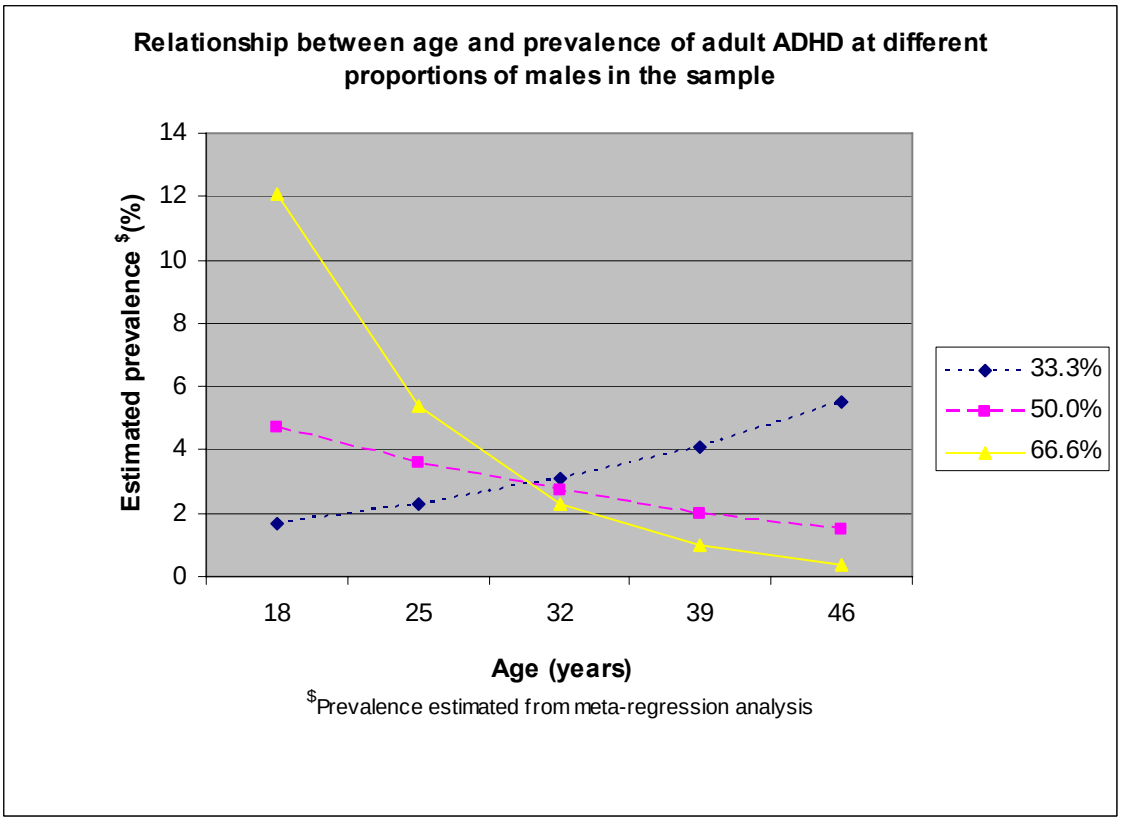


Figure 2B



Figures 2A and B: Relationship between gender composition (% of males) and prevalence (%) of adult ADHD. Meta-regression analysis indicated that gender and mean age, interacting with each other, were statistically significantly related to ADHD's prevalence in the sample (see text for detailed description of results). To illustrate the interaction for both factors, relationship of prevalence with gender composition and age are portrayed separately. In particular, Figure 2A illustrates the relationship between gender composition and prevalence for various ages (at 20, 30, 40 years) whereas Figure 2B shows the relationship between age and prevalence as a function of gender composition (i.e. one-third, one-half, two-thirds males).

4.2. Results of the Hungarian study estimating the prevalence of adult ADHD

4.2.1. Patient disposition and demographic data

During the screening phase 3529 subjects were recruited for the study. Out of 279 subjects who had screened positive on the short version of ASRS, 161 gave informed consent and were interviewed. Basic demographic data and the ASRS mean scores of the study sample, as well as the 'positively screened', 'interviewed' and 'not-interviewed' subsamples are presented in Table 10.

The entire study sample and the subsamples did not differ significantly in age. With regard to gender distribution, there was a small difference between the 'positively screened' subsample (61.51% females) and the rest of the sample (70.25% females), which reached statistical significance due to the large sample size (χ^2=8.35; p=0.0038). We examined the association between gender and ASRS score in the study sample and found that females had slightly higher score on the screener (females: M=13.5, SD=3.6 vs. males: M=13.3, SD=3.5); the difference did not reach statistical significance [F(1;3510)=3.41, p=0.065].

ASRS score was associated with age in the study sample indicating that higher score on ASRS tended to co-occur with younger age. However, the strength of the association was clinically rather modest (Pearson r = -0.055; p=0.0012), and obtained statistical significance as a result of the large sample size.

Among positively screened subjects, the 'interviewed' and the 'not-interviewed' subsamples did not differ significantly concerning age and gender. Although a significant difference was found between these two subsamples on the mean score of the screener, the direction of the difference showed that the 'interviewed' subsample tended to have slightly higher screener score than the 'not-interviewed' subsample. The observed difference was characterized by rather small effect size (approximately 1 point difference on a scale [ASRS screener] with a range of 0 - 24 points). Therefore, the clinical significance of this association concerning prevalence estimates is considered to be negligible.

Table 10. Basic demographic data and ASRS screener score of the study sample

	Study sample (N=3529)	*Positively screened (n=279)*	*Interviewed (n=161)*	*Not-interviewed (n=118)*
Gender [female n(%)]	2195 (62.2)	196 (70.25)*	119 (73.91)	77 (65.25)
Age Mean (SD)	40.47 (12.41)	40.95 (12.2)	41.45 (11.89)	40.26 (12.64)
ASRS[a] Mean (SD)	13.46 (3.61)	20.12 (2.68)	20.6 (2.74)	19.48 (2.46)

*= p=0.0038; significant difference between positively screened subsample and the study sample

a= Adult Self-Report Rating Scale; 6-item screener; score ranges between 0 and 24

For the 'interviewed' subsample, further demographic characteristics including marital status and years of education were available; these variables were not associated with ADHD diagnostic status. Gender, age and ASRS score, however, showed significant association with ADHD status (Table 11.). Results indicated that in the ADHD_DSM-IV diagnostic group, females were underrepresented and subjects were significantly younger compared with those without ADHD.

Separate analyses were conducted to evaluate the association between gender and ADHD diagnostic status in each diagnostic group. Females were consistently and significantly underrepresented in all diagnostic groups compared with the rest of the 'interviewed' subsample. Specifically, ADHD_DSM-IV (n=29) had 51.72% females vs

78.79% in the rest of the 'interviewed' subsample (n=132) [χ^2=9.03; p=0.0027]; similarly, ADHD_No-onset (n=33) had 51.52% females vs. 79.69% (n=128) [χ^2=10.80; p=0.0010]; ADHD_Sx-full (n=61) had 62.3% females vs. 81% (n=100) [χ^2=6.88; p=0.0087]; ADHD_Sx-reduced (n=68) had 64.71% females vs. 80.65% (n=93) [χ2=5.18; p=0.0229].

A logistic regression analysis was carried out for further investigation of the association between gender, age and ADHD diagnostic status. This analysis showed a significant effect of both demographic variables on ADHD diagnostic status [χ^2=14.46; p=0.0007], however there was no significant interaction between the effect of gender and age [Estimate: -0.031, Standard Error: 0.043, χ^2=0.5124; p=0.4741].

Table 11. Association between basic demographic data, ASRS screener score and ADHD status of the interviewed subsample (n=161)

	ADHD_DSM-IV (n=28)	*No ADHD_DSM-IV (n=131)*	*Statistics*
Gender [female n(%)]	15 (51.72)	104 (78.79)	χ^2=9.03 p=0.0027
Age [Mean (SD)]	35.31 (10.03)	42.81 (11.86)	F(1;158)=10.0 p=0.0019
Years of Education [Mean (SD)]	12.55 (2.7)	12.81 (3.07)	F(1;159)=0.18 p=0.68
Marital status [n(%)]			χ^2=5.20
0=single	12 (41.38)	28 (21.37)	p=0.16
1=married	11 (37.93)	66 (50.38)	
2=divorced	5 (17.24)	28 (21.37)	
3=widow	1 (3.45)	9 (6.87)	
ASRS [Mean (SD)]	22.28 (2.87)	20.23 (2.58)	F(1;152)=13.93 p=0.0003

4.2.2. Prevalence estimates

Observed (raw) data, crude prevalence and prevalence estimates adjusted for the sensitivity and specificity of the screener, are summarized in Table 12. for each of the diagnostic groups defined in our study.

A corrected estimate of prevalence of adult ADHD was also calculated by accounting for the 'not-interviewed' subsample. In particular, since raw data were unavailable for those who did not participate in the interview phase of the study, crude prevalence of adult ADHD for this subsample was estimated using three alternative approaches. First, we adopted the crude prevalence estimate from the 'interviewed' sample as a default estimate for the 'not-interviewed' sample (positively screened with no observed data for the final diagnostic status). Second (and third), for the purpose of sensitivity analyses, for the latter group we applied, respectively, the lower and the upper values of the Confidence Interval of the crude prevalence rate of the 'ADHD_DSM-IV' diagnostic group.

Using the crude (pooled) prevalence rates from the 'interviewed' subsample (based on available raw data) and the 'not-interviewed' subsample (based on estimation) adjusted prevalence estimate of adult ADHD was calculated for the entire study sample. These adjusted prevalence estimates are summarized in Table 13., and Figure 3. The sample was stratified by age and gender because of the previously described effect of these variables on ADHD diagnostic status. For the purpose of age stratification we applied the median age of the sample (40.5 years), thus two strata were described: subjects ≤ 40 years old and subjects >40 years old.

Table 12. Crude prevalence rates and prevalence estimates after adjusting for sensitivity and specificity data of the screener (n=161)

			Crude estimate adjusted for specificity and sensitivity data of the screener %(CI)		
Diagnostic group	***Raw data n (%)***	***Crude estimate[5] % (CI)***	*Estimate based on expected value %*	*Estimate based on upper CI of expected value %*	*Estimate based on lower CI of expected value %*
DSM-IV[1]	29 (18.01)	1.4 (1.0-1.81)	1.35 (0.40-2.86)	2.14 (1.0-3.89)	0.7 (0.15-2.0)
No onset[2]	33 (20.50)	1.62 (1.2-2.0)	1.64 (0.63-3.24)	2.46 (1.3-4.3)	0.95 (0.07-2.34)
Sx full[3]	61 (37.89)	3.0 (2.43-3.56)	3.65 (2.27-5.84)	4.58 (3.03-7.04)	2.78 (1.56-4.72)
Sx reduced[4]	68 (42.24)	3.34 (2.75-3.93)	4.16 (2.69-6.50)	5.09 (3.44-7.7)	3.26 (1.95-5.34)

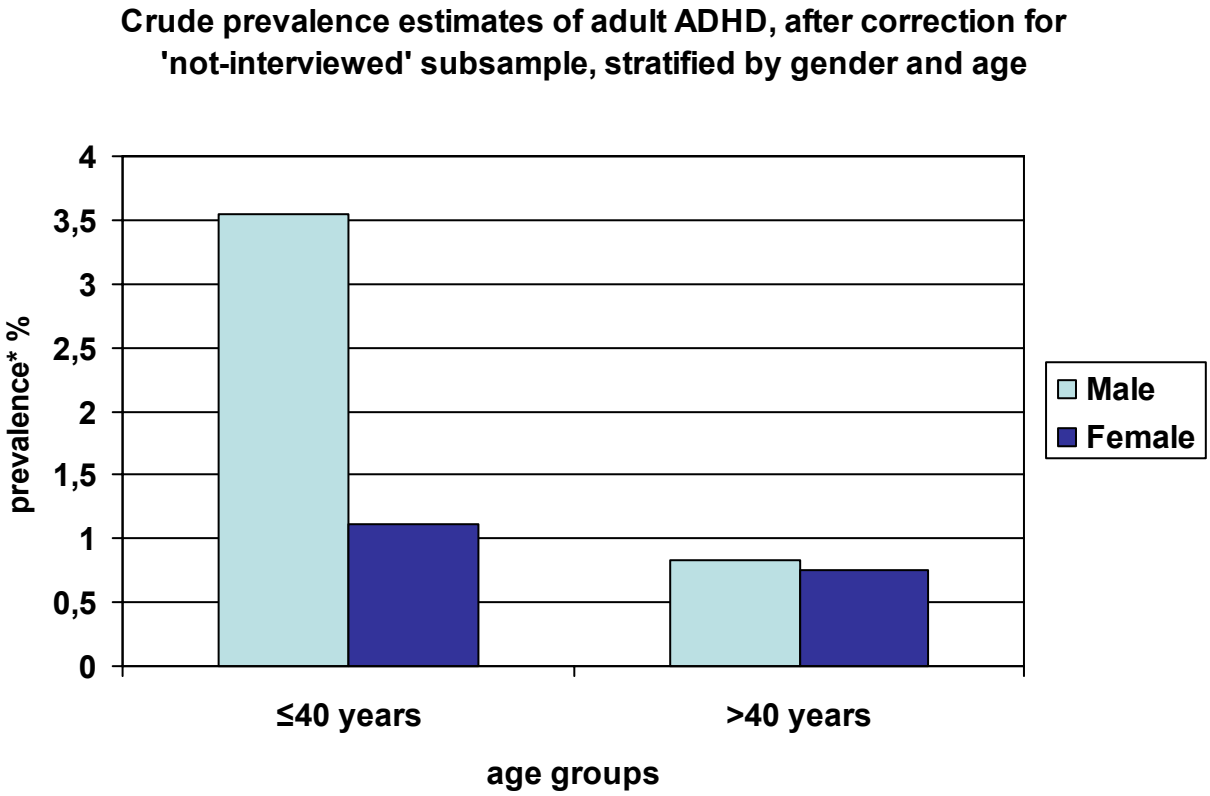
[1]*:* DSM-IV criteria for both childhood and adult ADHD with supporting background information based on the clinical interview. [2]*:* DSM-IV criteria for both childhood and adult ADHD, excluding onset criterion. [3]*:* DSM-IV symptom criterion only (6 of the 9 symptoms of either inattention or hyperactivity/impulsivity) for both childhood and adult ADHD. [4]*:* reduced number of symptoms present from DSM-IV symptoms (4 of 9 symptoms of either inattention or hyperactivity/impulsivity) in adulthood, while in childhood original DSM-IV symptom criterion had to be present.

[5]: Based on observed values on the' interviewed' subsample

Table 13. Crude and adjusted prevalence estimates after correction for ’not-interviewed’ subsample, stratified by gender and age

	Male	*Female*	*≤40 years*	*>40 years*
Crude prevalence estimate based on expected value (%)	2.07	1.12	1.88	0.98
Crude estimate adjusted for specificity and sensitivity data of the screener, based on estimated value (%)	2.3	0.91	2.02	0.70

Figure 3.



Adjusted prevalence estimate of adult ADHD for the entire study sample, based on crude (pooled) prevalence rates from the ‘interviewed’ subsample (based on available raw data) and the ‘not-interviewed’ subsample (based on estimation); corrected for the sensitivity and specificity data of the screener and stratified by age and gender. For the purpose of age stratification we applied the median age of the sample (40.5 years), thus two stratum were described: subjects ≤ 40 years old and subjects >40 years old.

5. Discussion

5.1. Population based studies estimating the prevalence of ADHD in adults

Population based studies estimated 1-7.3% prevalence of adult ADHD applying DSM-IV criteria (35;40;54;62-66;68;69;78). These studies typically used a large sample and therefore they were usually appropriate for estimating prevalence with sufficient precision. However, they did not assure representativeness since they were based on a sample of convenience. In general, the mean age of the subjects was low compared to a typical adult population, and there were several studies where the gender proportion of the sample was significantly unbalanced. In addition, the diagnostic tools and the approach for the identification of cases usually varied from study to study.

Gadow et al (71) provided estimates of the prevalence of adult ADHD using a large, representative sample of the general population. Nevertheless, because these authors applied only modified diagnostic criteria, their prevalence data are difficult to compare with the prevalence estimates from other studies that relied on the original DSM-IV classification.

The previously described two studies by Kessler et al (US) and Fayyad et al (multinational) did not provide crude estimates for the prevalence of adult ADHD in their sample (65;66). They used indirect estimation in order to assess the prevalence of adult ADHD in the general population. In both studies prevalence estimates were based on multiple imputation, using a combination of directly interviewed cases and multiply imputed cases from the remainder of the sample. All cases (directly interviewed and multiply imputed) in both samples were between the ages of 18 and 44; prevalence estimates for higher age ranges were based on weighting data (Fayyad et al, (66); Kessler et al, (65)). The aforementioned indirect estimations - applied in both studies - of the prevalence of adult ADHD in the general population, hinge on prediction equations that were obtained in a relatively small sample of subjects (n=154). It is not clear how reliably these prediction equations can predict the occurrence of ADHD, and what the exact predictors are. With regard of the multinational study it must be noted that the prediction equation of the US sample was extrapolated to other countries, a potential limitation pointed out by the authors. We note that a third study (Medina-Mora

et al (68)), conducted as part of the above-mentioned WHO survey and the multinational study, estimated the 12-month prevalence of ADHD in Mexico; however, similar to the parent study it did not provide a crude prevalence estimate for the targeted sample, and therefore was not included in the current meta-analysis.

In summary, the results of the studies in the literature trying to estimate the prevalence of adult ADHD yielded a high variability of their estimates (35;54;62-66;68;69). After reviewing the pertinent publications, we assumed that the variability of results may come from various – above detailed - methodological and diagnostic differences among these studies. In addition, only self-reports were used as a source of information and in some studies there was a lack of information about the relevant childhood symptoms that would be necessary for the proper diagnosis of adult ADHD (63;64;67).

5.2. Prevalence of adult ADHD

5.2.1.Meta-analysis

Our finding of 2.5% (95% CI: 2.1%-3.1%) pooled prevalence of adult ADHD seems to be conservative in the context of the relevant literature. For example, Kessler et al (65) and Fayyad et al (66) reported a prevalence of 4.4% of adult ADHD in the US study, and 3.4% prevalence in the multinational study described above. Our pooled prevalence estimates were derived from studies that provided data for crude prevalence based on DSM-IV criteria for diagnosing ADHD. In the above mentioned two studies, however, indirect estimates were derived based on assessing ADHD symptoms in childhood, and asking only a single question about the persistence of problems with ADHD in adulthood.

Polanczyk et al (1) recently estimated the Worldwide Prevalence of ADHD based on a meta-regression analysis of 102 articles of child and adolescent ADHD. Although the pooled prevalence of ADHD in children and adolescents according to Polanczyk et al (1) was 5.29%, these authors also reported that the prevalence in adolescents was around 3%. This estimate is consistent with our pooled prevalence data

especially in light of the finding about the relationship between age and prevalence of ADHD.

5.2.2. First Hungarian epidemiologic study

This study provided the first estimates on the occurrence of ADHD among Hungarian adults, evaluating a population of Hungarian GP practices. Prevalence of adult ADHD in this population, based on full DSM-IV diagnostic criteria, is in line with the result of our meta-analysis of prevalence rates. Our result is also comparable to the 1% prevalence estimate reported by Kooij et al., applying DSM-IV diagnostic criteria in a similar setting (62).

However, prevalence rates found in the present study appear somewhat lower than those reported from the US (3-5%) and the previously described multinational study, in which the average cross-national prevalence rate was 3.4%.

Interestingly, if we observe the findings of the multinational study, prevalence rates show a significant difference based on the countries' economical status. Specifically, prevalence rates are lower in lower income countries than in higher income countries (Table 5.). DSM-IV based Hungarian prevalence rate is rather in line with those reported from lower income countries. Nevertheless, another interesting observation is that while in case of The Netherlands, direct prevalence estimation based on a probability sample, but weighted according to the general population's age and gender distribution, thus providing generalisability, resulted in 1% (62), while indirect estimation in the multinational study resulted in 5% (66). Data from Mexico, on the other hand resulted opposite: direct estimation in a probability sample was 5.3% (35) and indirect estimation in the multinational study was 1.9% (66).

As it was discussed earlier, diagnostic approaches next to other methodological differences (e.g. sample selection, direct vs indirect estimations etc.) might be at the background of such high variability of the results of population based epidemiologic studies. Moreover, it has been already argued in the literature that DSM-IV diganostc criteria are not developmentally appropriate and are overly restrictive.

Therefore, in the first Hungarian epidemiologic study we applied different alternative diagnostic criteria in order to examine how these alternative diagnostic

criteria affect the prevalence estimates and to let our prevalence estimates be comparable to those previously published in the literature based on different diagnostic approaches. Specifically, we defined an 'ADHD_No-onset' group, in which DSM-IV diagnostic criteria were relaxed with not applying the age of onset criterion (i.e., symptoms present before the age of 7); an 'ADHD_full/Sx' group, in which we applied only the symptom threshold criterion of DSM-IV (≥6 symptoms - of either inattention or hyperactivity/impulsivity or both - present both in childhood and in adulthood); and an 'ADHD_reduced/Sx' group, in which we applied a further relaxed DSM-IV symptom threshold criterion (≥4 symptoms - of either inattention or hyperactivity/impulsivity or both - present in adulthood, ≥6 symptoms present in childhood). Based on our results, these alternative diagnostic groups resulted in higher prevalence rates in the study sample, following the gradual relaxation of the diagnostic criteria.

In particular, the 'ADHD_No-onset' group showed the least and 'ADHD_reduced/Sx' group showed the highest increase in prevalence compared to the 'ADHD_DSM-IV' diagnostic group. Interestingly, although prevalence estimates increased substantially, they remained within the range of prevalence rates found in previous studies based on only DSM-IV criteria. The observed increase of prevalence estimates, parallel to modification of diagnostic criteria, in our study was comparable to what was found in the study of Kooij et al, in a similar setting. These authors found that after relaxing the diagnostic threshold from 6 symptoms to 4 symptoms, prevalence rate increased from 1% to 2.5% (62). A possible reason for why prevalence rates did not show extreme increase along the relaxation of the diagnostic criteria might be that in most of other studies - which estimated directly the prevalence of adult ADHD – retrospective childhood ADHD was not assessed, or only assessed with regard to certain symptoms, while in our study we assessed retrospective childhood ADHD rigorously, based on clinical interview and full DSM-IV criteria.

When comparing the prevalence rate found in this study based on the 'ADHD_full/Sx' diagnostic group, with studies in which only symptom-based DSM-IV criteria were applied, results were similar: specifically 2.78-4.58% in this study versus 4% in a study among university students (64) and 4.7% in a sample of subjects applying for driving license (69).

Prevalence rates estimated in this Hungarian epidemiologic study suggest that even when the most restrictive diagnostic criteria are applied ADHD is highly prevalent among Hungarian adults. Although, with the restricitive diagnostic criteria prevalence rate is at the lower end of international estimate ranges we must note that the prevalence rate of even 1.35% is similar to the prevalence of schizophrenia (87;88).

5.3. Identified correlates of the prevalence of adult ADHD: gender and age

In our epidemiologic study females were consistently and significantly underrepresented in all diagnostic groups. In the background of this phenomenon we found a significant effect of gender on ADHD diagnostic status. Additionally, significant association of ADHD status with age was also found, showing that in the present sample the prevalence rate of DSM-IV based diagnosis of adult ADHD was reduced in the > 40 years stratum compared with the ≤ 40 years stratum. These observations together are in line with the result of our meta-analysis which found a complex effect of age and gender on the prevalence of adult ADHD when applying DSM-IV diagnostic criteria. Specifically, that while in younger age groups prevalence increases, in older age groups prevalence decreases when females are underrepresented in the sample and vica versa. Although results of our epidemiologic study seem to support these findings the interaction model tested by logistic regression analysis did not show significant interaction between the effect of age and gender, which may be attributable, at least in part, to the small sample size available for this analysis. Furthermore, the effect of age on the prevalence of adult ADHD has to be interpreted cautiously as well, since this was a cross-sectional study and the sample size was small in the ADHD_DSM-IV subsample.

A growing number of studies indicate that biased samples might be in the background of extreme gender effects on the prevalence of ADHD in clinically referred pediatric study samples. Specifically, some of these studies suggest that a weaker association with conduct disorder and disruptive behaviour in females compared to males might result in lower numbers of female referrals (89-91). In contrast to the clinical samples, where even 10 to 1 male: female ratio had been observed (92;93),

community samples showed a less extreme gender ratio (male:female risk being 3:1) in the prevalence of ADHD in childhood (90;91).

Compared to pediatric and adolescent studies, adult ADHD studies have generally showed more balanced distribution of prevalence in males and females. This may be attributable to the fact that, while childhood referrals are usually indicated by parents or teachers, in adulthood self-referrals are common. The observation that adult women with ADHD have more internalizing problems than men, which leads to a higher rate of self-referrals in adulthood (94), may, at least in part, explain the more balanced gender ratio in adult samples.

In the studies that were included in our meta-analysis, samples were community based, and the authors found heterogenous gender ratios, but no significant gender effect on prevalence in their samples, when applying DSM-IV diagnostic criteria (35;54;62-64;69). In two studies that were not included in our meta-analysis due to the lack of crude prevalence data (65;66), the authors found modest gender effects on prevalence, with significantly higher proportion of men in their ADHD group.

In spite of the findings of the studied articles that support no significant gender effects on prevalence, based on raw data of the individual studies, we identified gender as another factor that has an impact on the prevalence of adult ADHD. In this case – as in the case of effect of age - we presume that methodological differences and questions concerning sample selection and case identification are at the background of no, or modest appearance of gender effects in community based samples. In particular, our finding concerning the gender effect on prevalence estimates provides a new approach toward the criticism of the DSM-IV diagnostic criteria, when applied in adults. The finding, that prevalence might decrease with age when females are underrepresented in a sample while prevalence might increase with age when females are predominant in a sample, suggests the emergence of "new" cases – a phenomenon which cannot be interpreted in the context of a developmental disorder. We think that this finding rather implies the inappropriateness of case identification. In particular, based on our finding regarding the association of prevalence estimate with age and gender, it is conceivable that the DSM-IV diagnostic criteria function differently across age groups, identifying less females in lower age-groups and less males in the higher age groups. Another possible explanation would be that these "new" cases might refer, at least in part, to the

above mentioned possible „pseudo-new cases" of ADHD, when those female ADHD subjects who were not referred to treatment in childhood due to the lack of disruptive behavior problems refer themselves in adulthood, due to emerging comorbid psychiatric diseases.

Our findings indicate that the prevalence of adult ADHD has a significant negative association with age, although this association is moderated by the gender composition of the sample. The explanation and the potential practical use of this finding is complex.

Specifically, available literature and clinical experience indicate a modulation of the presentation of symptoms of ADHD by adulthood (53;95;96). Actual conceptualization of ADHD as a developmental disorder entails that, while the disabling feature of the disorder remains, both the quality and the severity of symptoms may change over time. Thus, applying the diagnostic criteria created for children may not be appropriate in adulthood. The developmental nature of the disorder also means that, whereas new cases do not emerge in adulthood, there might be a certain number of children who „outgrow" the disorder. This theoretical conceptualization predicts reduced prevalence in adulthood because of the nature of the disorder. Based on our presented result concerning the significant age-gender interaction, this conceptualization might be dominantly true for male ADHD cases with more hyperactive symptoms and linked disruptive behavioral problems in childhood compared with female ADHD subjects in general, since these symptoms show definite decline with age based on numerous findings in the literature (42;96).

While several studies reported that symptoms of ADHD decline with age (54;64-66;69;97), functional impairment and low socioeconomical outcome can be detected even with a reduced number of symptoms (1;31;62;66;95). These observations lead us to another possible conclusion suggesting that some children with ADHD do not outgrow ADHD but „outgrow the diagnostic criteria" (Barkley et al, (2)), meaning that reduced prevalence data among adults results from an underestimation of the real prevalence of adult ADHD.

Based on the literature there are two other factors concerning the diagnosis of adult ADHD that have to be mentioned since both of them may result in underestimating the prevalence of ADHD. In particular, the source of information

during the diagnostic process and the symptom recall that is needed for the retrospective childhood diagnosis. Several authors pointed out that collecting data with retrospective self-report would underestimate the prevalence of adult ADHD, since adults do not remember their childhood symptoms and might fail to judge their behavioral problems properly in the past, as well as in the present (2;98;99). ADHD was consistently associated with structural and functional abnormalities of the prefrontal cortex, including impairments of the executive functions(9;10;12-14;100). These structures and functions are involved in self-reflection and self-awareness, which are necessary for proper symptom recall and judgment of behavior. It is conceivable that poor symptom recall and poor judgement of oneself might be a consequence of the disorder itself and thus, result in an underestimation of the occurrence of the diagnosis when the diagnostic procedure hinge on only self-reports.

The Milwaukee study (2) – relevant also to clinical experience - showed that the source of information might have a great impact on diagnosing ADHD. According to the results of the Milwaukee study (2) the persistence of ADHD was 5-9 times higher based on parent's report than based on self report, and parent's report also showed higher potential to predict functional impairment than did self-report.

Concerning symptom recall, empirical findings are inconsistent (2;98;99;101-107). In the Milwaukee follow-up study (2) at the adult follow-up only 47% of the subjects showed childhood ADHD from the original ADHD index group. Their self-report showed only 20% concordance with their parents' report concerning their childhood symptoms (2).

Manuzza et al (98) on the other hand, taking the results of the New York follow-up study, reported a good symptom recall (the sensitivity of retrospective diagnosis of ADHD was 0.78, the specifity was 0.89) based on self-reports in the index group at the adult follow-up. These authors noted that this might result from the fact that subjects in the index group were from a clinically referred sample. Moreover, they suggested that adults who were not hospitalized in their childhood might have poorer symptom recall (98). The fact that in the New York study there was a high rate of false positive cases in the control group, according to Manuzza et al (98), raises the possibility of problematic symptom recall among non-ADHD subjects.

5.4. Limitations

We must note that the small number of studies included in the meta-regression analysis and the above detailed methodological difficulties of the reviewed and analysed studies are also potential limitation of our findings.

Results of the epidemiologic study have to be interpreted in light of certain limitations as well. First, since in the present study a sample of convenience was collected, prevalence estimates cannot be generalized for the entire population. Second, during the diagnostic procedure only self-report was available. Third, there was a relatively large refusal rate (29.4%) among positively screened subjects for further participation in the study. However, the refusal rate observed in our study is comparable to those reported in the literature (66), and its impact was addressed via sensitivity analyses. These analyses indicated that the prevalence estimates remained robust to the changing of input parameters in a broad range (i.e., when we applied the upper and lower 95% confidence limits of the observed proportion prevalence for the 'not-interviewed' subsample in order to estimate the prevalence for the entire target population).

Another possible limitation of our study is that including subjects in GPs' office might introduce a selection bias. Based on the current data, it can not be inferred whether people with ADHD would be underrepresented in this population due to their difficulties in waiting hours in a waiting room because of their hyperactive and impulsive symptoms, or, conversely, people with ADHD would be overrepresented due to more frequent health problems. Based on published data about the outcome and impairments associated with adult ADHD it can be suggested that adults with ADHD are more prone for accidents, showing more health related problems and lower level of self-care compared with non-ADHD peers, which would result in more frequent visits at the GP (32;108). Notably, the prevalence estimates of Kooij et al (62), which were also based on a GP population, similarly to our results, are in the lower end within the prevalence range published in the literature.

6. Conclusions

One of our main objectives was to estimate the prevalence of adult ADHD for the first time, in a large Hungarian community sample. In summary, prevalence rates found in the Hungarian study population are somewhat more conservative, but still are in line with those reported previously in the literature. Notably, even when the most restrictive diagnostic criteria are applied ADHD is highly prevalent among Hungarian adults. In particular, prevalence rate of even 1.35% is similar to the prevalence of schizophrenia.

We assume that our reported prevalence rates indirectly support the validity of ADHD diagnosis in adults, taking into consideration the previously mentioned lack of both public and professional awareness of this disorder.

Another objective was to investigate how do different diagnostic criteria affect the prevalence estimates of adult ADHD, in the same Hungarian GP population. Relaxing DSM-IV diagnostic criteria with regard to the age-onset criterion as well as the symptom threshold increased the prevalence estimates. Although prevalence estimates increased substantially, they remained within the range of prevalence rates found in previous studies based on only DSM-IV criteria. This might be due to the rigorous data assessment and setting, especially with regard to retrospective childhood ADHD diagnosis. This latter observation suggest that next to diagnostic criteria, other factors, such as design, setting, assessment methods also play a key role in prevalence estimation and might have contributed to the high variability of reported prevalence estimates. Another factor, that needs further clarification is cultural and/or economical influence on the occurrence (or identification) of ADHD cases in adults, since we have found that our prevalence estimates are closer to estimates from lower income countries, which are significantly lower compared with estimates from higher income Western-European countries and the US. This notion, speculatively, might be linked with the previously mentioned effect of professional awareness and attentional preference as well as public awareness of the disorder.

A further objective was to pool the prevalence estimates published in the literature and to identify correlates of the prevalence of adult ADHD by employing a meta-analytic approach. Based on our meta-regression analyisis, the pooled prevalence

of adult ADHD was 2.5% and we identified a complex effect of gender and age on the prevalence estimates. In particular, our finding is consistent with the suggestion that the prevalence of ADHD declines with age, however this association is mediated by gender. The background of this phenomenon remains unclear and a caveat is needed in this regard. Specifically, the lack of validity of DSM-IV diagnostic criteria for diagnosing adult ADHD is an important issue, emerging both from the interpretation of our findings and also from the relevant literature. It seems that the DSM-IV criteria in the diagnosis of adult ADHD functions differently across age groups and gender and thus, may underestimate the prevalence of the disorder in adults.

We found the effect of gender and age on prevalence rates also in the epidemiologic study, however, the interaction between these two effects could not be detected most probably because of the small sample size.

Taking together our results and previously described findings in the literature it can be suggested that further investigations are necessary to find out in what proportion methodological issues or natural developmental features are responsible for the observed decline in the prevalence of ADHD with age. Future well-designed, community-based epidemiological studies critically depend on an improved understanding of the etiology and pathophysiology of the disorder, which in turn would help to improve the current diagnostic criteria and would thereby facilitate a more reliable identification of patients with ADHD.

7. Summary

In spite of the growing literature of adult ADHD, relatively little is known about the prevalence and correlates of adult ADHD. Thus, the main objective of my thesis was to estimate the prevalence of adult ADHD and identify certain demographic correlates based on a meta-analysis of the available prevalence data in the literature, and based on a direct estimation on a large Hungarian community sample. For the meta-analysis we used Medline, Psychlit and Embase databases as well as hand search to find relevant publications and applied a mixed-effect meta-regression technique. In the Hungarian study, subjects between 18 and 60 years were included in the screening phase of the study (N=3529), conducted in 17 GP practices in Budapest. Out of 279 positively screened subjects 161 subjects participated in a clinical interview and filled out a self-report questionnaire to confirm the diagnosis. Beside DSM-IV diagnostic criteria, we applied four alternative diagnostic criteria: 'No-onset' (DSM-IV criteria without the specific requirement for onset); Sx/full (DSM-IV "symptoms only" criteria); and Sx/reduced (DSM-IV "symptoms only" criteria with a reduced threshold for symptom count). The pooled prevalence of adult ADHD was 2.5% (95% CI: 2.1%-3.1%). Gender and mean age, interacting with each other, were significantly related to ADHD's prevalence. Meta-regression analysis indicated that the proportion of subjects with ADHD decreases with age when males and females are equally represented in the sample. In the Hungarian study crude prevalence estimates adjusted for the specificity and sensitivity data of the screener were 1.35% in the 'DSM-IV' group, 1.64% in the 'No-onset' group, 3.65% in the 'Sx/full' group and 4.16% in the 'Sx/reduced' group. Logistic regression analysis showed that ADHD was significantly more prevalent with younger age and male gender [χ^2=14.46; p=0.0007]. Prevalence estimates corrected for the 'not-interviewed' subsample and adjusted for specificity and sensitivity data of the screener was 2.3% in males, 0.91% in females; 2.02% in the ≤40 years age group and 0.70% in the > 40 years age group, based on DSM-IV diagnostic criteria. In conclusion, prevalence rates found in the Hungarian study are somewhat lower, but still are in line with those reported in the literature. Based on our findings, prevalence of ADHD in adults declines with age in the general population. We think, however, that the unclear validity of DSM-IV diagnostic criteria for diagnosing adult ADHD can lead to reduced prevalence rate by the underestimation of the prevalence of adult ADHD.

Összefoglalás

A felnőttkori ADHD-ról már nagy mennyiségű adat gyűlt össze az irodalomban, mégis igen keveset tudunk a gyakoriságáról és a prevalenciát befolyásoló tényezőkről. Disszertációm fő célkitűzése ezért az volt, hogy megbecsüljem a felnőttkori ADHD prevalenciáját és azonosítsak a prevalenciát befolyásoló tényezőket, egyrészt a rendelkezésre álló irodalmi adatok meta-analízisével, másrészt egy direkt lakossági szűrés segítségével, magyar háziorvosi praxisokban. A meta-analízis során a Medline, Psychlit és Embase adatbázisok alapján, illetve kézi kereséssel azonosítottuk a releváns publikációkat, majd meta-regressziós technikát alkalmaztunk az adatok elemzéséhez. A 17 magyar háziorvosi praxis bevonásával végzett epidemiológiai vizsgálat során 18 és 60 év közötti lakosokat vontunk be (N= 3529) a szűrővizsgálatba. A 269 kiszűrt, feltételezett ADHD-s személyből 161 esetében tudtuk elvégezni a részletes klinikai interjút és egy diagnosztikus kérdőív felvételét az ADHD diagnózisának megerősítéséhez. A diagnózis alkotás során a DSM-IV diagnosztikai kritériumok mellett alternatív kritériumokat is alkalmaztunk: 'No-onset' (DSM-IV kritériumok a megjelenés életkori kritériumát kivéve); Sx/full (csak a DSM-IV tünettani kritériumai); and Sx/reduced (csak a DSM-IV tünettani kritériumai, de csökkent tünetszám küszöböt alkalmazva). A meta-analízis alapján, az ADHD felnőttkori prevalenciája 2.5% (95% CI: 2.1%-3.1%). Az életkor és a nem, egymással interakcióban, szignifikánsan összefüggött a prevalenciával. A meta-regressziós elemzés alapján az ADHD-s személyek aránya az életkorral csökken, amennyiben a mintában kiegyensúlyozott a nők és a férfiak aránya. A magyar vizsgálatban, a nyers prevalencia adatokat korrigáltuk a szűrőteszt szenzitivitása és specificitása alapján, így a prevalencia 1.35% volt a 'DSM-IV' csoportban, 1.64% a 'No-onset' csoportban, 3.65% a 'Sx/full' csoportban és 4.16% a 'Sx/reduced' csoportban. Az ADHD gyakorisága szignifikánsan magasabb volt fiatalabb korban és férfiak esetében [χ^2=14.46; p=0.0007]. A prevalencia adatokat korrigáltuk a 'nem- interjúzott' alminta figyelembe vételével is. Az ADHD prevalenciája így 2.3% volt férfiak körében, 0.91% nők körében; 2.02% a 40 alatti csoportban és 0.70% a 40 év feletti csoportban, a DSM-IV kritériumok alapján. Összefoglalva, a magyar vizsgálat eredményei valamivel konzervatívabb prevalencia értéket mutattak, de jól illeszkedtek az irodalomban eddig publikált adatokhoz. Eredményink arra utalnak, hogy az ADHD prevalenciája az életkorral csökken az

általános populációban, azonban véleményünk szerint ennek hátterében felmerül, hogy a - felnőttek körében nem validált - DSM-IV diagnosztikai kritériumrendszer alapján alkotott diagnózis alulbecsüli az ADHD gyakoriságát felnőttekben.

8. Reference List

1. Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. (2007) The Worldwide Prevalence of ADHD: A Systematic Review and Metaregression Analysis. Am J Psychiatry, 164:942-948.

2. Barkley RA, Fischer M, Smallish L, Fletcher K. (2002) The Persistence of Attention-Deficit/Hyperactivity Disorder into Young Adulthood As a Function of Reporting Source and Definition of Disorder. J Abnorm Psychol, 111:279-289.

3. Rasmussen P, Gillberg C. (2000) Natural Outcome of ADHD With Developmental Coordination Disorder at Age 22 Years: a Controlled, Longitudinal, Community-Based Study. J Am Acad Child Adolesc Psychiatry, 39:1424-1431.

4. Yan WW. (1998) An Investigation of Adult Outcome of Hyperactive Children in Shanghai. Psychiatry Clin Neurosci, 52 Suppl: S303-S305.

5. Mannuzza S, Klein RG, Bonagura N, Malloy P, Giampino TL, Addali KA. (1991) Hyperactive Boys Almost Grown Up. Arch Gen Psychiatry, 48:77-83.

6. Mannuzza S, Klein RG, Addali KA. (1991) Young Adult Mental Status of Hyperactive Boys and Their Brothers: A Prospective Follow-Up Study . J Am Acad Child Adolesc Psychiatry, 30:743-751.

7. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. (1998) Adult Psychiatric Status of Hyperactive Boys Almost Grown Up. Am J Psychiatry, 155:494-498.

8. Weiss G, Hechtman L, Milroy T, Perlman T. (1985) Psychiatric Status of Hyperactives As Adults: A Controlled Prospective 15 Year Follow-Up of 63 Hyperactive Children. J Child Psychol Psychiatry, 24:211-220.

9. Bush G, Valera EM, Seidman LJ. (2005) Functional Neuroimaging of Attention-Deficit/Hyperactivity Disorder: a Review and Suggested Future Directions. Biol Psychiatry, 57:1273-1284.

10. Seidman LJ, Valera EM, Makris N. (2005) Structural Brain Imaging of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry, 57:1263-1272.

11. Castellanos FX, Lee PP, Sharp W, Feffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL. (2002) Developmental Trajectories of Brain Volume Abnormalities in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. JAMA, 288:1740-1748.

12. Roth RM, Saykin AJ. (2004) Executive Dysfunction in Attention-Deficit/Hyperactivity Disorder: Cognitive and Neuroimaging Findings. Psychiatr Clin N Am, 27:83-96.

13. Hesslinger B, Tebartz van Elst L, Thiel T, Haegele K, Henning J, Ebert D. (2002) Frontoorbital Volume Reductions in Adult Patients With Attention Deficit Hyperactivity Disorder. Neurosci Lett, 328:319-321.

14. Spencer TJ. (2008) Neurobiology and Genetics of ADHD in Adults. CNS Spectr, 13(Suppl 13): 5-7.

15. Spencer TJ, Biederman J, Madras BK, Dougherty DD, Bonab AA, Livni E, Meltzer PC, Martin J, Rauch S, Fischman AJ. (2007) Further Evidence of Dopamine Transporter Dysregulation in ADHD: a Controlled PET Imaging Study Using Altropane. Biol Psychiatry, 62:1059-1061.

16. Faraone SV, Biederman J, Spencer T, Wilens T, Seidman LJ, Mick E, Doyle AE. (2002) Attention-Deficit/Hyperactivity Disorder in Adults: an Overview. Biol Psychiatry, 48:9-20.

17. Sonuga-Barke EJ. (2005) Causal Models of Attention-Deficit/Hyperactivity Disorder: From Common Simple Deficits to Multiple Developmental Pathways. Biol Psychiatry, 57:1231-1238.

18. Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffmann JM, Kilts CD. (2000) Alterations in the Functional Anatomy of Working Memory in Adult Attention Deficit/Hyperactivity Disorder. Am J Psychiatry, 157:278-280.

19. Seidman LJ, Biederman J, Webwe W, Hatch M, Faraone SV. (1998) Neuropsychological Function in Adults With Attention Deficit Hyepractivity Disorder. Biol Psychiatry, 44:260-268.

20. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. (2005) Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: a Meta-Analytic Review. Biol Psychiatry, 57:1336-1346.

21. Bálint S, Czobor P, Komlósi S, Mészáros Á, Simon V, Bitter I. (2009) Attention Deficit Hyperactivity Disorder (ADHD): Gender- and Age-Related Differences in Neurocognition. Psychol Med, 39:1337-1345.

22. Muller BW, Gimbel K, Keller-Pliessnig A, Sartory G, Gastpar M, Davids E. (2007) Neuropsychological Assessment of Adult Patients With Attention-Deficit/Hyperactivity Disorder. Eur Arch Psychiatry Clin Neurosci, 257:112-119.

23. Bálint S, Czobor P, Mészáros Á, Simon V, Bitter I. (2008) [Neuropsychological Impairments in Adult Attention Deficit Hyperactivity Disorder: a Literature Review]. Psychiatr Hung, 23:324-335.

24. Peterson K, McDonagh MS, Fu R. (2008) Comparative Benefits and Harms of Competing Medications for Adults With Attention-Deficit Hyperactivity Disorder: a Systematic Review and Indirect Comparison Meta-Analysis. Psychopharmacology (Berl), 197:1-11.

25. Mészáros Á, Czobor P, Bálint S, Simon V, Bitter I. (2007) [Pharmacotherapy of Adult Attention Deficit/Hyperactivity Disorder (ADHD): a Systematic Review]. Psychiatr Hung, 22:259-270.

26. Pliszka S. (2007) Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry, 46:894-921.

27. Nutt DJ, Fone K, Asherson P, Bramble D, Hill P, Matthews K, Morris KA, Santosh P, Sonuga-Barke E, Taylor E, Weiss M, Young S. (2007) Evidence-Based Guidelines for Management of Attention-Deficit/Hyperactivity Disorder in Adolescents in Transition to Adult Services and in Adults: Recommendations From the British Association for Psychopharmacology. J Psychopharmacol, 21:10-41.

28. Mészáros Á, Czobor P, Bálint S, Komlósi S, Simon V, Bitter I. (2009) Pharmacotherapy of Adult Attention Deficit Hyperactivity Disorder (ADHD): a Meta-Analysis. Int J Neuropsychopharmacol, 12:1137-1147.

29. Kessler RC, Adler L, Ames M, Barkley RA, Birnbaum H, Greenberg P, Johnston JA, Spencer T, Üstün TB. (2005) The Prevalence and Effects of Adult Attention Deficit/Hyperactivity Disorder on Work Performance in a Nationally Representative Sample of Workers. J Occup Environ Med, 47:565-572.

30. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. (1993) Adult Outcome of Hyperactive Boys. Educational Achievement, Occupational Rank, and Psychiatric Status. Arch Gen Psychiatry, 50:565-576.

31. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. (2006) Functional Impairments in Adults With Self-Reports of Diagnosed ADHD: A Controlled Study of 1001 Adults in the Community. J Clin Psychiatry, 67:524-540.

32. Stein MA. (2008) Impairment Associated With Adult ADHD. CNS Spectr, 13(Suppl 12):9-11.

33. Adler LA. (2008) Epidemiology, Impairments, and Differential Diagnosis in Adult ADHD: Introduction. CNS Spectr, 13 (Suppl 12):4-5.

34. Sobanski E, Bruggemann D, Alm B, Kern S, Deschner M, Schubert T, Philipsen A, Rietschel M. (2007) Psychiatric Comorbidity and Functional Impairment in a Clinically Referred Sample of Adults With Attention-Deficit/Hyperactivity Disorder (ADHD). Eur Arch Psychiatry Clin Neurosci, 257:371-377.

35. Almeida Montes LG, Hernandez Garcia AO, Ricardo-Garcell J. (2007) ADHD Prevalence in Adult Outpatients With Nonpsychotic Psychiatric Illnesses. J Atten Disord, 11:150-156.

36. Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, Mick E, Lehman BK, Doyle A. (1993) Patterns of Psychiatric Comorbidity, Cognition, Psychosocial Functioning in Adults With Attention Deficit Hyperactivity Disorder. Am J Psychiatry, 150:1792-1798.

37. Sobanski E. (2006) Psychiatric Comorbidity in Adults With Attention-Deficit/Hyperactivity Disorder (ADHD). Eur Arch Psychiatry Clin Neurosci, 256 (Suppl 1): i26-i31.

38. Birnbaum HG, Kessler RC, Lowe SW, Secnik K, Greenberg PE, Leong SA, Swensen AR. (2005) Costs of Attention Deficit-Hyperactivity Disorder (ADHD) in the US: Excess Costs of Persons With ADHD and Their Family Members in 2000. Curr Med Res Opin, 21:195-206.

39. Schoffski O, Sohn S, Happich M. (2008) [Overall Burden to Society Caused by Hyperkinetic Syndrome (HKS) and Attention Deficit Hyperactivity Disorder (ADHD)]. Gesundheitswesen 70:398-403.

40. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington DC, American Psychiatric Association, 1994.

41. Adler L, Barkley RA, Newcorn JH. (2008) ADHD and Comorbid Disorders in Adults. J Clin Psychiatry, 69:1328-1335.

42. Brassett-Harknett A, Butler N. (2007) Attention-Deficit/Hyperactivity Disorder: An Overview of the Etiology and a Review of the Literature Relating to the

Correlates and Lifecourse Outcomes for Men and Women. Clinical Psychology Review, 27:188-210.

43. Wender PH. Attention-Deficit Hyperactivity Disorder in Adults. New York, Oxford University Press, 1995.

44. McGough JJ, Barkley RA. (2004) Diagnostic Controversies in AdultAttention Deficit Hyperactivity Disorder. Am J Psychiatry, 161:1948-1956.

45. Ward MF, Wender PH, Reimherr FW. (1993) The Wender Utah Rating Scale: an Aid in the Retrospective Diagnosis of Childhood Attention Deficit Hyperactivity Disorder. Am J Psychiatry, 150:885-890.

46. Murai Z, Porkoláb N, Simon V, Telek T, Bitter I. (2005) Felnőttkori Figyelemhiányos/ Hiperaktív Zavar (Felnőttkori ADHD) Irodalmi Áttekintés. Orvostovábbképző Szemle, Különszám:18-39.

47. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Second Edition. Washington DC., American Psychiatric Association, 1968.

48. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington DC., American Psychiatric Association, 1980.

49. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC., American Psychiatric Association, 1987.

50. Barkley RA, Biederman J. (1997) Toward a Broader Definition of the Age-of-Onset Criterion for Attention-Deficit Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry, 36:1204-1210.

51. Faraone SV, Doyle AE. (2001) The Nature and Heretability of Attention-Deficit/Hyperactivity Disorder. Child Adolesc Psychiatry Clin N Am, 10:299-316.

52. Philipsen A, Richter H, Peters J, Alm B, Sobanski E, Colla M, Munzebrock M, Scheel C, Jacob C, Perlov E, Tebartz van EL, Hesslinger B. (2007) Structured Group Psychotherapy in Adults With Attention Deficit Hyperactivity Disorder: Results of an Open Multicentre Study. J Nerv Ment Dis, 195:1013-1019.

53. Weiss M, Weiss J. (2004) A Guide to the Treatment of Adults With ADHD. J Clin Psychiatry, 65(suppl. 3):27-37.

54. Faraone SV, Biederman J. (2005) What Is the Prevalence of Adult ADHD? Results of a Population Screen of 966 Adults. J Atten Disord, 9:384-391.

55. Morrison JR, Stewart MA. (1971) A Family Study of the Hyperactive Child Syndrome. Biol Psychiatry, 3:189-195.

56. Cantwell DP. (1972) Psychiatric Illness in the Families of Hyperactive Children. Arch Gen Psychiatry, 27:414-417.

57. Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT. (1990) Family-Genetic and Psychosocial Risk Factors in DSM-III Attention Deficit Disorder. J Am Acad Child Adolesc Psychiatry, 29:526-533.

58. Schachar R, Wachsmuth R. (1990) Hyperactivity and Parental Psychopathology. J Child Psychol Psychiatry, 31:381-392.

59. Faraone SV, Biederman J, Chen WJ, Krifcher B, Keenan K, Moore C. (1992) Segregation Analysis of Attention Deficit Hyperactivity Disorder: Evidence for Single Gene Transmission. Psychiatric Genetics, 2:255-275.

60. Crosbie J, Schachar R. (2001) Deficient Inhibition As a Marker for Familial ADHD. Am J Psychiatry, 158:1884-1890.

61. Gittelman R, Mannuzza S. (1985) Hyperactive Boys Almost Grown Up. Arch Gen Psychiatry, 42:937-947.

62. Kooij JJ, Buitelaar JK, van den Oord EJ, Furer JW, Rijnders CA, Hodiamont PP. (2005) Internal and External Validity of Attention-Deficit Hyperactivity Disorder in a Population-Based Sample of Adults. Psychol Med, 35:817-827.

63. DuPaul GJ, Schaughency EA, Weyandt LL, Tripp G, Kiesner J, Ota K, Stanish H. (2001) Self-Report of ADHD Symptoms in University Students: Cross-Gender and Cross-National Prevalence. J Learn Disabil, 34:370-379.

64. Heiligenstein E, Conyers LM, Berns AR, Smith MA. (1998) Preliminary Normative Data on DSM-IV Attention Deficit Hyperactivity Disorder in College Students. J American College Health, 46:185-188.

65. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demier O, Faraone SV, Greenhill LI, Howes MJ. (2006) The Prevalence and Correlates of Adult ADHD in the United States: Results From the National Comorbidity Survey Replication. Am J Psychiatry, 163:716-723.

66. Fayyad J, De Graaf R, Kessler RC, Alonso J, Angermeyer M, Demyttenaere K, De Girolamo G, Haro JM, Karam EG, Lara C, Lépine J-P, Ormel J, Posada-Villa J, Zaslavsky AM, Jin R. (2007) Cross-National Prevalence and Correlates of Adult Attention-Deficit Hyperactivity Disorder. Br J Psychiatry, 190:402-409.

67. Weyandt LL, Linterman I, Rice JA. (1995) Reported Prevalence of Attentional Difficulties in a General Sample of College Students. J of Psychopathology and Behavioral Assesment, 17:293-304.

68. Medina-Mora ME, Borges G, Lara C, Benjet C, Blanco J, Fleiz C, Villatoro J, Rojas E, Zambrano J. (2005) Prevalence, Service Use, and Demographic Correlates of 12-Month DSM-IV Psychiatric Disorders in Mexico: Results From the Mexican National Comorbidity Survey. Psychol Med, 35:1773-1783.

69. Murphy K, Barkley RA. (1996) Prevalence of DSM-IV Symptoms of ADHD in Adult Licensed Drivers: Implication for Clinical Diagnosis. J Atten Disord, 1: 147-161.

70. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. J Clin Psychiatry, 59 (Suppl 20):22-33.

71. Gadow KD, Sprafkin J, Schneider J, Nolan EE, Schwartz J. (2007) ODD, ADHD, Versus ODD+ADHD in Clinic and Community Adults. J Atten Disord, 11:374-383.

72. DuPaul GJ. (1991) Parent and Teacher Rating of ADHD Symptoms: Psychometric Properties in a Community Based Sample. J Clin Child Psychol, 20:245-253.

73. Norvilitis JM, Ingersoll T, Zhang J, Jia S. (2008) Self-Reported Symptoms of ADHD Among College Students in China and the United States. J Atten Disord, 11:558-567.

74. Barkley RA, Murphy K. Attention deficit hyperactivity disorder: A clinical workbook. New York, Guilford, 1998.

75. Kessler RC, Merikangas KR. (1998) The National Comorbidity Survey Replication (NCS-R): Design and Field Procedures. Int J Methods Psychiatric Res, 13:60-68.

76. Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, Angermeyer MC, Bernert S, de Girolamo G, Morosini P, Polidori G, Kikkawa T, Kawakami N, Ono Y, Takeshima T, Uda H, Karam EG, Fayyad JA, Karam AN, Mneimneh ZN, Medina-Mora ME, Borges G, Lara C, de Graaf R, Ormel J, Gureye O, Shen Y, Huang Y, Zhang M, Alonso J, Haro JM, Vilagut G, Bromet EJ, Gluzman S, Webb C, Kessler RC, Merikangas KR, Anthony JC, Von Korff MR, Wang PS, Brugha TS, Aguilar-Gaxiola S, Lee S, Heeringa S, Pennel BE, Zaslavsky AM, Üstün TB, Chatterji S, WHO World Mental Helath Survey Consortium. (2004) Prevalence, Severity, and Unmet Need for Treatment of

Mental Disorders in the World Health Organization World Mental Health Surveys. JAMA, 291:2581-2590.

77. Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, Howes MJ, Jin R, Secnik K, Spencer T, Ustun TB, Walters EE. (2005) The World Health Organization Adult ADHD Self-Report Scale (ASRS): a Short Screening Scale for Use in the General Population. Psychol Med, 35:245-256.

78. Barbaresi W, Katusic S, Colligan R, Weaver A, Pankratz V, Mrazek D, Jacobsen S. (2004) How Common Is Attention-Deficit/Hyperactivity Disorder? Towards Resolution of the Controversy: Results From a Population-Based Study. Acta Paediatr Suppl, 93:55-59.

79. van Houwelingen HC, Arends LR, Stijnen T. (2002) Advanced Methods in Meta-Analysis: Multivariate Approach and Meta-Regression. Statist Med, 21: 589-624.

80. DerSimonian R, Laird N. (1986) Meta-Analysis in Clinical Trials. Controlled Clinical Trials, 7:177-188.

81. Desu MM, Raghavarao D. Sample Size Methodology. New York, Academic Press, 1990.

82. Machin D, Campbell M, Fayers P, Pinol A. Sample Size Tables for Clinical Studies, 2nd Edition. Malden MA, Blackwell Science, 1997.

83. Hahn GJ, Meeker WQ. Statistical Intervals. New York, John Wiley & Sons, 1991.

84. Bíró S.(editor). A DSM-IV-TR diagnosztikai kritériumai. Budapest, Animula Kft. 2000.

85. Gart JJ, Buck AA. (1966) Comparison of a Screening Test and a Reference Test in Epidemiologic Studies. II. A Probabilistic Model for the Comparison of Diagnostic Tests. Am J Epidemiol, 83:593-602.

86. Hardy RJ, Thompson SG. (1996) A Likelihood Approach to Meta-Analysis With Random Effects. Stat Med, 15:619-629.

87. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. (1994) Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States. Results From the National Comorbidity Survey. Arch Gen Psychiatry, 51:8-19.

88. Regier DA, Farmer ME, Rae DS, Myers JK, Kramer M, Robins LN, George LK, Karno M, Locke BZ. (1993) One-Month Prevalence of Mental Disorders in the United States and Sociodemographic Characteristics: the Epidemiologic Catchment Area Study. Acta Psychiatr Scand, 88:35-47.

89. Biederman J, Kwon A, Aleardi M, Chouinard VA, Marino T, Cole H, Mick E, Faraone SV. (2005) Absence of Gender Effects on Attention Deficit Hyperactivity Disorder: Findings in Nonreferred Subjects. Am J Psychiatry, 162:1083-1089.

90. Biederman J, Faraone SV, Monuteaux MC, Bober M, Cadogen E. (2004) Gender Effects on Attention-Deficit/Hyperactivity Disorder in Adults, Revisited. Biol Psychiatry, 55:692-700.

91. Gaub M, Carlson CL. (1997) Gender Differences in ADHD: A Meta-Analysis and Critical Review. J Am Acad Child Adolesc Psychiatry, 36:1036-1045.

92. Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Wilens TE, Frazier E, Johnson MA. (2002) Influence of Gender on Attention Deficit Hyperactivity Disorder in Children Referred to a Psychiatry Clinic. Am J Psychiatry, 59:36-42.

93. Arnold L. (1999) Sex Differences in ADHD: Conference Summary. J Abnorm Child Psychol 38:555-569.

94. Gershon J. (2002) A Meta-Analytic Review of Gender Differences in ADHD. J Atten Disord, 5:143-154.

95. Wender PH, Wolf LE, Wasserstein J. (2001) Adults With ADHD: an Overview. Annals of the New York Academy of Sciences, 931:1-16.

96. Biederman J, Mick E, Faraone SV. (2000) Age-Dependent Decline of Symptoms of Attention Deficit Hyperactivity Disorder: Impact of Remission Definition and Symptom Type. Am J Psychiatry, 157:816-818.

97. Hill JC, Schroener EP. (1996) Age-Dependent Decline of Attention Deficit Hyperactivity Disorder. Am J Psychiatry, 153:1143-1146.

98. Mannuzza S, Klein RG, Klein DF, Bessler A, Shrout P. (2002) Accuracy of Adult Recall of Childhood Attention Deficit Hyperactivity Disorder. Am J Psychiatry, 159:1882-1888.

99. Wolkind S, Coleman EZ. (1983) Adult Psychiatric Disorder and Childhood Experiences: the Validity of Retrospective Data. Br J of Psychiatry, 143:188-191.

100. Barkley RA. (1997) Behavioral Inhibition, Sustained Attention, and Executive Functions: Constructive Theory of ADHD. Psychol Bull, 121:65-94.

101. Ericsson KA, Simon HA. (1980) Verbal Reports As Data. Psychol Rev, 87:215-251.

102. Nisbett RE, Wilson TD. (1977) Telling More Than We Know. Psychol Rev, 74:231-259.

103. Robins LN. (1985) Epidemiology: Reflections on Testing the Validity of Psychiatric Interviews. Arch Gen Psychiatry, 42:918-924.

104. Schaffer D. (1994) Attention Deficit Hyperactivity Disorder in Adults. Am J Psychiatry, 151:633-638.

105. Yarrow MR, Campbell JD, Burton RV. (1970) Recollections of Childhood. Monogr Soc Res Child Dev, 35:1-83.

106. Henry B, Moffitt TE, Caspi A, Langley J, Silva PA. (1994) On the "Remembrance of Things Past". Psychol Assess, 6:92-101.

107. Holmshaw J, Simonoff E. (1996) Retrospective Recall of Childhood Psychopathology. Int J Methods Psychiatric Res, 6:79-88.

108. Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustun TB, Zaslavsky AM. (2005) Patterns and Predictors of Attention-Deficit/Hyperactivity Disorder Persistence into Adulthood: Results From the National Comorbidity Survey Replication. Biol Psychiatry, 57:1442-1451.

9. List of publications

9.1. Publications linked to the topic of the dissertation

Murai Z, Porkoláb N, Simon V, Telek T, Bitter I. (2005) Felnőttkori figyelemhiányos/ hiperaktív zavar (Felnőttkori ADHD) - Irodalmi áttekintés. Orvostovábbképző Szemle, suppl 18-39.

Simon V, Czobor P, Bálint S, Mészáros Á, Murai Z, Bitter I. (2007) A Felnőttkori Figyelemhiányos/Hiperaktivitási Zavar (Attention Deficit/Hyperactivity Disorder – ADHD) Epidemiológiai Vizsgálatainak Részletes Áttekintése. Psychiatr Hung, 22:4-19.

Mészáros Á, Czobor P, Bálint S, Simon V, Bitter I. (2007) A felnőttkori figyelemhiányos/hiperaktivitás zavar (ADHD) gyógyszeres kezelésének hatékonysága: irodalmi áttekintés. Psychiatr Hung, 22:259-70.

Bálint S, Czobor P, Komlósi S, Mészáros Á, Simon V, Bitter I. (2009) Attention Deficit Hyperactivity Disorder (ADHD): Gender- and age-related differences in neurocognition. Psychol Med, 39:1337-1345.

Bálint S, Czobor P, Mészáros Á, Simon V, Bitter I. (2008) A felnőttkori figyelemhiányos hiperaktív zavarban tapasztalható neuropszichológiai deficit: irodalmi áttekintés. Psychiatr Hung, 23:324-335.

Simon V, Czobor P, Bálint S, Mészáros Á, Bitter I. (2009) Prevalence and correlates of adult ADHD – a meta-analysis. Br J Psychiatry, 194:204-211.

Mészáros Á, Czobor P, Bálint S, Komlósi S, Simon V, Bitter I. (2009) Pharmacotherapy of adult attention deficit hyperactivity disorder (ADHD): a meta-analysis. Int J Neuropsychopharmacol, 12:1137-1147.

Bitter I, Simon V, Bálint S, Mészáros Á, Czobor P. (2009) How do different diagnostic criteria, age and gender affect the prevalence of Attention Deficit Hyperactivity

Disorder in adults? An epidemiological study in a Hungarian community sample. Eur Arch Psychiatry Clin Neurosci, DOI: 10.1007/s00406-009-0076-3.

9.2. Pulblications independent from the topic of the dissertation

Simon V, Sik Lányi C, Simon L. (2004) Using virtual public transport for treating phobias. Int J on Disability and Human Development, 4:211-215.

Simon V, De Hert M, Wampers M, Peuskens J, Van Winkel R. (2009) The relation between neurocognitive dysfunction and impaired insight in patients with schizophrenia. Eur Psychiatry, 24:239-243.

Simon V, Van Winkel R, De Hert M. (2009) Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? – A literature review. J Clin Psych, 70:1041-1050.

De Hert M, Simon V, Vidovic D, Franic T, Wampers M, Peuskens J, Van Winkel R. (2009) Evaluation of the association between insight and symptoms in a large sample of patients with schizophrenia. Eur Psychiatry, DOI: 10.106/j.eurpsy.2009.04.004.

Book chapters**:**

Sík Lányi C, Laky V, Tilinger Á, Pataky I, Simon L, Kiss B, Simon V, Szabó J, Páll A. Developing Multimedia Software and Virtual Reality Worlds and their Use in Rehabilitation and Psychology, Transformation of Healthcare with Information Technologies, IOS Press, 2004, pp. 273-284.

Sik Lányi C, Simon V, Pataky I, Kosztyán Zs T, Mátrai R: Medical Applications of Virtual Reality Worlds and Multimedia, Overcoming the barries to e-health growth in Enlarged Europe, Health and Management Press, Krakow, 2004, pp. 189-204.

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