CHAPTER 1

GENERAL INTRODUCTION
William, aged 73 years, sitting in a wheelchair was brought into the clinic by his son who was being treated for Attention-Deficit/Hyperactivity Disorder (ADHD) and depression. William was recovering from a broken hip, but because of his restlessness and difficulty sitting still the recovery was going slower than could be expected. His rehabilitation doctor was familiar with ADHD and suggested diagnostic testing and treatment for William, despite his old age.

William appeared to be dreary and lethargic for some time now; he frequently had had these episodes. William explained that he also had problems with concentrating, that he was easily distracted, had problems finishing things, and that he had troubles with listening. These problems started in his childhood and were still present. William did not finish high school; he started working at an early age and had had more than 30 different jobs. At these jobs he worked for short periods before leaving abruptly or because of arguments with his boss or co-workers. While he tried running his own business, he failed several times because of financial problems. Eventually his wife divorced him and his children grew up with her.

William was diagnosed with ADHD and recurrent depressive episodes. When treated with an anti-depressant and methylphenidate, his mood improved and the physical restlessness reduced quickly, which in turn resulted in a successful treatment of his broken hip.

The case of William clearly shows that Attention-Deficit/Hyperactivity Disorder (ADHD) can still be present at old age. Although it was first believed that ADHD was a childhood disorder and that its symptoms would fade out in adulthood, nowadays it is recognized that ADHD is a persistent disorder continuing into adulthood.\textsuperscript{1,2}

There are some concerns regarding the diagnosis and treatment of ADHD. In the 90s there was an increase in the diagnosis of ADHD and in the prescription of stimulants as treatment for ADHD in children and adults. This fuelled the discussion that ADHD was overdiagnosed and that stimulants were overprescribed. This upward trend however, appeared mainly to be associated with an increase in ADHD diagnosis and treatment in girls.\textsuperscript{3} The question remains however, what the consequences of ADHD are and which treatment works the best in older adults. Should older adults with ADHD even be treatment with medication? Exploratory research is needed to get insight into these questions.

Only recently, it is also shown that ADHD persists into old age and may have a profound impact on the lives of patients and their surroundings. However, little is known about the disorder in older adults. Clinical books, such as the Principles and Practice of Geriatric Psychiatry (2011) and the Dutch Handbook of Geriatric Psychiatry (Handboek ouderenpsychiatrie, 2011), have no reference to ADHD at all. Only very recently the first scientific papers on ADHD in older adults have been published. So, the diagnostics and treatment of ADHD in older adults is mainly based on what is known from younger adults and children, whereas it might be expected that due to aging and increasing somatic comorbidity the diagnostics and treatment of ADHD in older adults may need its own clinical guidelines. In order to obtain more knowledge about the prevalence and consequences of ADHD we developed a side study in the Longitudinal Aging Study Amsterdam. This resulted in the dissertation of Marieke Michielsen (2015) and the current dissertation.

In this dissertation I have investigated whether ADHD can be screened in older adults with a screener that is developed for younger adults. Furthermore, I have investigated the prevalence rate of ADHD in older adults, the lifetime stability of ADHD symptoms, and the effects of the disorder on physical and mental functioning.

**Clinical picture**
ADHD is characterized by an early onset in childhood and a lifelong pattern of inattentive symptoms, such as: making careless mistakes, quickly being distracted by own thoughts, having difficulties with organizing tasks and activities, being forgetful and losing important things; and/or hyperactive-impulsive symptoms, such as: having difficulty sitting still, feeling
restless inside, difficulty talking quietly, stepping over own boundaries and saying things without thinking first. These symptoms lead to impairments in several areas. For instance, education and work may be characterized by not completing education, a pattern of many short-lasting jobs, or under-performance at work. In relationships problems with sexuality, impulsively commencing or ending relationships, financial problems or gambling may occur. In social contacts people with ADHD may have difficulty maintaining social contacts, they may have low self-assertiveness, or difficulty initiating social contacts. During free time they may be unable to relax properly, to finish a book or watch a film all the way through, they may be sensation seeking and/or taking too many risks, or have contact with the police/the courts. Regarding self-confidence they may have a negative self-image due to experiences of failure, fear of failure in terms of starting new things, perfectionism, or excessive intense reaction to criticism.4

ADHD can be divided into three subtypes (based on DSM-IV-TR criteria): combined subtype (ADHD-C): at least six inattentive and six hyperactive-impulsive symptoms present; predominantly inattentive subtype (ADHD-IA): at least six inattentive symptoms, but less than six hyperactive-impulsive symptoms present; predominantly hyperactive-impulsive subtype (ADHD-HI): less than six inattentive symptoms, but at least six hyperactive-impulsive symptoms present.

Aetiology
Twin, adoption and family studies have shown that ADHD is transmitted in families, implicating a genetic cause. The heritability of the disorder is estimated to be 76%.5 The focus of genetic studies has mainly been on the neurotransmitters dopamine and norepinephrine since these two can be associated with the core symptoms of ADHD. Several candidate genes have been associated with ADHD: dopamine receptor D4 and D5 (DRD4, DRD5), dopamine transporter (DAT1), dopamine beta-hydroxylase (DBH), serotonin transporter (5-HTT), serotonin receptor 1B (HTR1B) and synaptosomal-associated protein 25 (SNAP-25).6 Alongside a genetic cause studies have shown that gene-environment interactions, such as pregnancy and delivery complications, prematurity, and maternal smoking during pregnancy, as well as severe neglect after birth raise the risk for ADHD.5,7–9

Prevalence
In order to establish possible needs for treatment for ADHD it is necessary to have credible data on the prevalence in all age groups. In a systematic review the prevalence rate of ADHD in children has been estimated to be 5.29%.10 In adults the prevalence rate of ADHD
is somewhat lower and is estimated to be around 4.4% (see Table 1). One of the few studies that includes older adults into their prevalence estimates, found a prevalence of ADHD of 1% – 2.5% in Dutch adults aged 18 to 75 years. A study from Sweden found prevalence rates of 3.3% of retrospectively reported childhood ADHD symptoms (based on a self-report symptom list) in older adults aged 65 – 80 years.

Table 1 Prevalence of ADHD and ADHD subtypes in children and adults

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
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<tbody>
<tr>
<td>ADHD (%)</td>
<td>5.29</td>
<td>4.4</td>
</tr>
<tr>
<td>ADHD-C (%)</td>
<td>1.9 – 3.6</td>
<td>0.9</td>
</tr>
<tr>
<td>ADHD-IA (%)</td>
<td>4.5 – 5.4</td>
<td>1.3</td>
</tr>
<tr>
<td>ADHD-HI (%)</td>
<td>1.7 – 2.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

ADHD = Attention-Deficit/Hyperactivity Disorder; ADHD-C = ADHD Combined subtype; ADHD-IA = ADHD inattentive subtype; ADHD-HI = ADHD hyperactive-impulsive subtype.

Since in most studies older adults were not included, little is known about the prevalence of ADHD diagnoses in this age group. Therefore, studying the prevalence of ADHD in older adults was one of the aims of this thesis.

Lifetime stability of ADHD symptoms

Several longitudinal studies have followed children into adulthood to get an understanding of the development and continuation of ADHD symptoms. These studies showed a relative reduction of the number of hyperactive-impulsive symptoms compared to the number of inattentive symptoms over time, with the inattentive symptoms causing more impairment in adulthood than hyperactive-impulsive symptoms. A substantial number of adults with childhood ADHD still meet the full diagnostic criteria for ADHD, whereas 50% meet critical for residual ADHD. This means that they do not meet the full diagnostic criteria for ADHD, but still have ADHD symptoms leading to impairment. Since life demands in adulthood are significantly different compared to childhood, some symptoms that are important in childhood may no longer be relevant in adulthood. In this line of reasoning the cut-off of the diagnostic criteria for ADHD in adults in the DSM-5 have been changed compared to the DSM-IV-TR. Instead of six or more ADHD symptoms being present in adulthood, the diagnosis is now based on five or more ADHD symptoms being present in adulthood. It is unknown whether the number and nature of ADHD symptoms in older adults should be the same as those in younger adults. Therefore it is important to examine whether the number and the nature of ADHD symptoms decreases in old age compared to the number and nature of ADHD symptoms in childhood. In addition, in older adults cognitive aging may interfere with or be
presented as ADHD symptoms. Cognitive changes, such as a decline in attention, working memory, and executive functioning are common in old age\textsuperscript{22} and could easily be interpreted as inattentive symptoms of ADHD. This may lead to false positive diagnoses of ADHD in older people. Therefore, the present thesis compared the change in symptoms of inattention over time among older adults with ADHD and those without ADHD.

Consequences/daily life of ADHD in adults

ADHD may have negative consequences during lifespan. Adults with ADHD are less likely to be employed, they have more job changes and are less likely to graduate from high school or obtain a college degree.\textsuperscript{23} They also report more problems with relationships,\textsuperscript{24} financial problems\textsuperscript{1} and high financial stress.\textsuperscript{25} When people grow older and stop working it may be expected that the consequences of ADHD decline because the daily demands change.

In most cases ADHD is accompanied by comorbid disorders such as mood and anxiety disorders, substance use disorders, conduct and oppositional defiant disorder, sleeping disorders and personality disorders.\textsuperscript{26–29} The question arises what the effects of ADHD may be on the physical health and mental functioning of older adults with the disorder.

Physical health

In children and younger adults the disorder has been linked to unhealthy life styles like smoking, and alcohol- and drug use. It has been shown that ADHD is a risk factor for developing a substance use disorder at an early age with a more severe and longer course of the substance abuse.\textsuperscript{27} It has also been found that approximately 80\% of the children and adults with ADHD may have a delayed sleep phase, which may lead to short sleep duration.\textsuperscript{28,29} To compensate for energy loss due to short sleep, greater food intake may lead to overweight; an increased prevalence of ADHD has been found in people who are obese.\textsuperscript{30–33} Higher rates of asthma have been found in children and adults with ADHD and an increased prevalence of ADHD has also been found in children and adults with asthma.\textsuperscript{34,35} Because of the chronic nature of ADHD, people with the disorder have a prolonged exposure to the unhealthy factors mentioned. It has been found that their healthcare use and costs are higher than in people without ADHD.\textsuperscript{28,29,36–40} Since aging comes with an increase in physical health problems it seems likely that older adults with ADHD may have unhealthy lifestyle behaviours and more physical diseases.
Cognitive functioning

Cognitive problems, such as poor attention and executive functioning are core deficits in ADHD. Cognitive functioning is well studied in children and adults with the disorder. In younger adults impaired cognitive functioning has been found in a wide range of domains such as attention, behavioural inhibition, executive functioning and memory. This is similar to the impairments that are found in children with ADHD. The relative similarity of impairments registered in children and younger adults may suggest a continuation of cognitive malfunctioning into old age. Only few studies included older adults with ADHD, however. Those that did focused on the association between ADHD and mild cognitive impairment and Alzheimer’s disease or dementia with Lewy body (DLB). Although no direct linkages have been found between ADHD and Alzheimer’s disease, significantly higher levels of preceding ADHD symptoms have been found in DLB patients when compared with controls or patients with Alzheimer disease.

The older brain may be more vulnerable for the effects of ADHD on cognitive functioning due to a diminished reserve capacity as a consequence of cognitive aging. This could lead to additional problems in cognitive functioning and to diagnostic confusion.

Life events and depression

It has been found that 20% to 70% of patients with ADHD also have comorbid depression. Depressive symptoms, recurrent brief depression or fully developed depressive episodes are reported by 35% – 50% of adults with ADHD. It is not yet fully understood why ADHD and depression are so strongly interrelated. It might be associated with negative life events that seem more prevalent in ADHD patients. Several studies and a meta-analyses showed negative life events to be associated with depressive symptoms in late life. Children and younger adults with ADHD report more negative life events than controls and since higher scores of ADHD are associated with more negative life events this may explain the relation between ADHD and depression. Since older adults are frequently exposed to various negative life events and have an increasing chance of experiencing negative life events, these events may contribute to the relation between ADHD and depression.

Screener

To detect ADHD in older adults a validated and brief screener might be helpful. Because a full diagnostic work-up for ADHD is expensive and time consuming, a validated and brief screener is highly relevant thus reducing the number of persons that need a full diagnostic
assessment. Validated and reliable ADHD screening instruments for older adults are unfortunately non-existent.

There are several rating scales that have been developed to identify ADHD in younger adults. In a recent review 14 scales for identifying ADHD in adults were assessed. The short version of the Wender Utah Rating Scale (WURS) and the Conners’ Adult ADHD Rating Scales (CAARS) showed the best psychometric properties and the authors discuss that this might be due to the fact that these two lists are not solely based on the DSM-IV criteria. As discussed before, the DSM-IV criteria for adult ADHD might be not specific enough to diagnose ADHD in adults.

In 2010 Barkley, Murphy and Fischer published another short questionnaire to be used in adults to screen for ADHD. They created a list of the most common complaints such as verbal impulsiveness, working memory, sense and use of time, emotional self-regulation, and planning and forethought. In addition, they added items that are often mentioned by adults with ADHD in clinical practice. To reduce the item set, they selected the complaints occurring in at least 65% of the ADHD-group and those that were significantly more present in the ADHD-group compared to the control group. Logistic regression was used to further reduce the list to an adequate item set for ADHD in adulthood. The final set consists of seven executive functioning items and two DSM-IV-TR criteria. Since this questionnaire was developed for young adults (mean age of 26 – 37 years), the present thesis examines the criterion validity of the questionnaire as a screener for detecting ADHD in older adults.

The aims of this thesis

- to study whether an ADHD screener that is developed for younger adults is also a valid screener in older adults;
- to study the prevalence of ADHD in older adults;
- to study the stability of ADHD symptoms over time;
- to study physical and cognitive functioning in older adults with ADHD;
- to study whether life event explain the association between depression and ADHD.

The Longitudinal Aging Study Amsterdam (LASA)

LASA is an on-going population-based study on the predictors and consequences of changes in physical, cognitive, emotional, and social functioning of older people in the Netherlands. A random sample of older men and women, stratified by age and sex according to the expected 5-year mortality, was drawn from the population registries of
eleven municipalities in three geographic areas of the Netherlands. Data-collection started in 1992 – 1993, and included follow-up measurements every three years. The ADHD study was embedded in the sixth cycle (2010 – 2011) of the LASA study.

All the findings of this thesis were obtained using data from LASA participants, which were collected using a two-phase sampling design. In Phase 1, the screening list was part of the regular LASA measurement. Data were collected of 1494 respondents of ages 60 to 101 years, 45 respondents were excluded at baseline due to greater than or equal to three missing values on the screener. For Phase 2, respondents were excluded when they showed cognitive decline (defined as a difference-score of more than one standard deviation (≥3 points) on the Mini Mental State Examination (MMSE) over the previous 3 years, low cognitive functioning (score ≤ 18), or a history of cerebrovascular accident. In Phase 2, 271 (18%) participants were selected based on their score on the screener. Scores were stratified into three levels: a high scoring group, most likely to have ADHD (score 3 – 9); a moderate scoring group (score 1 – 2) and the low scoring group (score 0). The participants from the low and moderate scoring groups were selected using a non-proportional stratified random sampling design. Ninety-four respondents of the low scoring group, 93 respondents of the moderate scoring group, and 84 respondents of the high scoring group were approached; 85 (90%), 80 (86%), and 69 (82.3%), respectively, consented to be interviewed. Three respondents were excluded from statistical analyses due to too many missing values (≥3), a cerebral vascular accident, or not being able to recollect childhood conditions. Thus, the study sample consisted in total of 231 participants.

Outline of this thesis

Chapter 2 focuses on the criterion validity of an ADHD screener in older adults developed by Barkley and Murphy for younger adults. Furthermore, the test-retest reliability was determined and the optimal cut-off score for identifying ADHD in older adults is reported.

Chapter 3 describes the estimation of the prevalence of ADHD in older adults. The Diagnostic Interview for ADHD in Adults, second edition (Diagnostisch interview voor ADHD bij volwassenen, DIVA 2.0) was used to assess the presence of all 18 DSM-IV-TR criteria and impairments in five areas of functioning (work, education, family, social/relationships, and self-confidence) in childhood and at present.

In Chapter 4 the lifespan stability of ADHD symptoms and ADHD subtypes are reported. We examined whether the decline in number of ADHD symptoms and change in the ratio of
Inattentive vs. hyperactive-impulsive symptoms found in younger adults can also be found in older adults.

In **Chapter 5** the association between ADHD, unhealthy lifestyles and the most prevalent chronic diseases (cardiac disease (including myocardial infarction), peripheral atherosclerosis, stroke, diabetes mellitus, chronic obstructive pulmonary disease (asthma, chronic bronchitis, or pulmonary emphysema), arthritis (rheumatoid arthritis or osteoarthritis) and cancer) in older adults is presented.

**Chapter 6** focuses on cognition and presents the results of the study into cognitive functioning of older adults with ADHD, which has been adjusted for concurrent depressive symptoms.

In **Chapter 7** the results are presented on the study into the role of adverse life events on the association between ADHD and depression in older adults.

Finally, in **Chapter 8** the results of the individual studies are interpreted and put into context. The overall findings are discussed, followed by implications for future research.