ADHD and atopic diseases
van der Schans, Jurjen

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 10
GENERAL DISCUSSION
The overall focus of this thesis was to assess the possible association between presence of drug-treated atopic disorders and ADHD and to contribute to a biopsychosocial model of psychotropic drug use by addressing three different research aims. The first aim of this thesis (chapters 2-4) was to assess the effectiveness and impact of psychotropic drug use in children. The first chapter reports on the differences in school performance in relation to various characteristics of psychotropic drug use. The second chapter looked at the persistence and adherence of methylphenidate, and the possible influence of atopic diseases. In the third chapter the cost-effectiveness of psychotropic drug use in children and adolescents was discussed. In the second and third section of this thesis (part II and III) I addressed both the association between ADHD and atopic diseases in children (chapter 5-7) and in adults (chapters 8-9).

This chapter summarizes the findings of each individual chapter. Combining the main findings per section and putting them in context of current literature further insight is given into the outcomes of each of the three main research questions. In the last section the strengths and limitations of the research projects will be discussed, and the possible clinical implications of our main findings. This thesis ends with the concluding remarks.

SUMMARY PER CHAPTER

Although psychotropic drugs like methylphenidate are known to reduce symptoms of ADHD of the related disorders, data on school performance among children using methylphenidate is limited. In chapter 2 the objective was to explore school performance among children using methylphenidate at the end of primary education. We linked data from a pharmacy prescription database with a standardized school achievement test. By doing so we could explore the association between test scores and different characteristics of methylphenidate use, like moment of initiation of treatment, dose of treatment, and concomitant treatment. The results of this study suggest that an earlier start of methylphenidate treatment is associated with lower school performance than children starting later with the treatment. This could indicate a limited effect of long-term treatment or a more strongly affected group of early starters. The study also indicates that children using methylphenidate still perform worse at school compared to their peers. In the next part of the section the focus was on the effectiveness of psychotropic drug use, chapter 3, and the association between atopic disease and the adherence and persistence of treatment with methylphenidate was assessed. By linking long-term prescription data of children being treated with methylphenidate with specific patient characteristics, possible risk factors contributing to methylphenidate non-persistence could be determined: atopic disease increases the risk of methylphenidate non-persistence in children. Older age, concomitant use of psychotropic drugs, and being prescribed short-acting methylphenidate also increased the risk of methylphenidate non-persistence.
In the last chapter of the first part of this thesis the societal impact of psychotropic drug use is addressed by combining treatment effects with related cost, calculated from a societal perspective. The objective of chapter 4 was to evaluate the cost-effectiveness of a switch from immediate-release methylphenidate (IR-MPH) to extended-release methylphenidate (ER-MPH) in children who are sub-optimally treated. Although IR-MPH is the medical treatment of first choice, the necessity to use several IR-MPH tablets per day and associated potential social stigma at school often leads to reduced compliance, sub-optimal treatment, discontinuation of treatment and therefore economic loss. This study showed that the long acting ER-MPH results in costs up to four times higher than the short acting IR-MPH. Despite the higher costs, the longer-term economic analysis indicated that switching sub-optimally treated patients from IR-MPH to ER-MPH is very likely to be cost-saving and more effective. The results of this analysis imply that over a period of 10 years, considerable cost-savings may be produced for the society and the health-care system.

The second part of this thesis zoomed in on the association between atopic diseases and ADHD in both children and adults. More knowledge about the possible involvement of atopy in the pathogenesis of ADHD could provide insight into possible approaches for the prevention, treatment, and progression of psychiatric disorders such as ADHD.

In chapter 5 the objective was to assess whether children with drug-treated ADHD are more likely to have received treatment for asthma, allergic rhinitis, or eczema before the start of ADHD medication use compared with controls. The second objective was to examine the effect of parents receiving medication for ADHD and atopic diseases on ADHD medication use in their offspring. By using medication proxies as a definition for both ADHD and atopic diseases, we conducted a retrospective nested case-control study. The results provided additional evidence to support the hypothesis that atopic disorders, such as asthma, increase the risk of developing ADHD. This evidence supports the hypothesis that there is a link between atopy and ADHD or that certain patients are more prone to health care seeking behavior and therefore more likely to receive atopy and ADHD medication. In the subsequent literature study presented in chapter 6, observational, cross-sectional, and longitudinal, studies were systematically reviewed that assessed the association between atopic disorders including asthma, atopic eczema, allergic rhinitis, and ADHD in children and adolescents. For longitudinal studies, a weighted odds ratio of these associations was estimated. The results provide strong evidence to support the hypothesis that the three main atopic diseases asthma, eczema, and allergic rhinitis are independently associated with ADHD in childhood and that individuals have on average a 30% to 50% greater chance of developing ADHD later in life compared with persons without these diseases.

The study in chapter 7 shifted focus from the association between atopy and ADHD on group level to individual patient data to determine the temporal order of the association. The study showed that atopic symptoms and sleeping problems may have a direct association with subsequent ADHD symptoms on an individual patient level. In addition, an association between symptoms of ADHD and sleep problems on atopy was also shown on an individual
In the last chapters of this thesis the focus was on the association between atopy and ADHD in adults. First, in chapter 8 it was shown that the use of ADHD medication has increased in the Netherlands over the last decade (2004-2014), especially in women where the prevalence rate increased from 0.9 to 5.7 per 1000. This high medication use in adults is not only the result of the continuation of treatment started in childhood, but also of a marked increase in the number of new adult users (0.5 to 1.5 new users per year per 1000 adults). Although the number of new users seems fairly constant since 2012, it is important to monitor future trends regarding the use of ADHD medications among adults because pharmacological options for treating ADHD in adults are being used on an off-label base.

In chapter 9 the association between atopy and ADHD in adults was determined in a large pharmacy prescription database looking at presence of both diseases, similar to the study in chapter 5, and the severity of asthma. It was found that the presence of rhinitis, eczema, is associated with ADHD in adults. The strength of the association was similar compared to that in children. However, we found a higher association between ADHD and a history of asthma, with similar results for the different asthma severity groups. Both ADHD and asthma have an early onset and it is therefore difficult to determine the effect of asthma on ADHD in adults or vice versa.

WHAT IS THE CLINICAL AND ECONOMIC IMPACT OF PSYCHOTROPIC DRUG USE IN CHILDREN?

The prevalence of psychiatric disorders is high. It is estimated that up to 10% of the overall disease burden across the lifespan can be attributed to mental health problems. Contrary to somatic diseases, which have the largest impact during late adulthood, psychiatric disorders peak during early adulthood. The impact of psychiatric disorders is also considerably larger in children and adolescents compared to other (somatic) diseases due to their high incidence and high prevalence rates in childhood. With an increased cure of especially communicable diseases the relative impact of global mental health will become even bigger in future years.

In 2011 the findings from the Grand Challenges in Global Mental Health initiative, a consortium of patients, researchers, clinicians, lawyers, and policy makers were published. This initiative announced a top 25 of research priorities for improvement of mental health around the globe. Four of these priorities directly relate to ADHD, i.e., clarifying the causes of the disorder, improving diagnosis and treatment, developing preventive strategies, and defining the global burden of disease. In the next sections the ADHD treatment with methylphenidate will be discussed related to multiple real life outcomes.
School performance and psychotropic drug use

Psychiatric disorders have a negative impact on academic functioning, which is largely accounted for by problems with inattention and conduct, and are associated with lower achievements in school. Most symptom patterns of psychiatric disorders are associated with impairment on emotional, cognitive, and social level. There is an ongoing discussion about the impact of psychotropic drugs, like psychostimulants and antipsychotics, on school performance. Overall, the literature suggests that pharmacotherapy of ADHD benefits children on the short term, especially when looking at behavioral improvements, while effects of pharmacotherapy of ADHD on academic performance vary between studies.

Our study into school performance and methylphenidate treatment in a large prescription database suggests that an earlier start of methylphenidate treatment is associated with lower school performance compared to children starting later with treatment. This could indicate that methylphenidate has a limited effect in long-term treatment or that the group who started treatment earlier was more severely affected. Unfortunately, no information concerning ADHD severity was available for this study. However, dosing of methylphenidate, which could be interpreted as an indirect measurement of ADHD severity, was not associated with school performance. The long-term effects of methylphenidate on school performance could therefore be questioned by the results of this study. Because both continuation and performance at school are important factors in the improvement of behavioral problems like ADHD, but also in the future perspectives in the development of the child, it is essential to monitor the long-term effectiveness of treatment, taking into account the academic achievement of the child, the treatment goals of the parents, but especially the goals of the child. If there is no effect of treatment on an essential factor like school performance, it should be questioned whether treatment is desirable. This may prevent unnecessary, prolonged, and unwanted drug use in children. Regular evaluations of treatment goals and assessment of treatment effectiveness by planning medication holidays could contribute to a more adequate therapy.

The results of this thesis also indicate that methylphenidate treatment in children does not normalize school performance. This remains true even after statistical adjustment for factors like household income, concurrent treatment, and ethnicity, which are associated with lower school performance. Because it is not clear if this result is clinically relevant, future research into the normalizing effect of ADHD treatment if any is warranted and could indicate a need for future treatment developments. Studies have shown that although factors related to academic performance, like academic productivity, may improve with the use of stimulant medication, an increase of quality of the academic performance is not seen. This is confirmed by a study that showed a distinction between an increase of executive functioning without a clear clinical improvement. If stimulant treatment is mainly influencing academic productivity instead of academic performance, the misuse of stimulants and ethics of cognitive enhancement of children need to be considered in the discussion regarding the effects of pharmacotherapy in children with ADHD.
Adherence and methylphenidate use

Patient compliance is one of the most common problems in the treatment of ADHD, and persistence and adherence to ADHD treatment is generally low. Untreated or sub-optimally treated ADHD can lead to significant problems in both academic and social setting. Overall, the discontinuation rate of ADHD treatment varies but can be up to 84% within a 12-months period. Multiple factors related to the medication but also to the patient itself, like age, are associated with adherence problems and discontinuation of treatment. One of these factors that is associated with treatment discontinuation is the presence of comorbidities. Besides common psychiatric comorbidities, atopic diseases are often present in children, but little is known about the association with treatment discontinuation and non-persistence. The results in chapter 3 provide evidence that atopic diseases may increase the risk of methylphenidate non-persistence in children. Whether the association between atopic diseases and treatment non-persistence should be implemented into the management of ADHD is dependent on the underlying cause of the non-persistence of treatment. Without a clear association between the two diseases findings could indicate a more general problem with the concomitant use of multiple drugs. If there is an association between atopic diseases and ADHD the treating physician should be more alert on treatment adherence when a comorbid atopic disease is present in ADHD. The association between atopic diseases and ADHD will be discussed in the last sections of this discussion.

Cost-effectiveness of methylphenidate use in children

When looking at the outcome of methylphenidate treatment it is not only essential to determine the real-life effectiveness of the treatment but also consider costs. In the field of health-economy the objective is to determine the maximum value for money by combining the assessment of clinical effectiveness with the related costs. By assessing the cost-effectiveness of a treatment, it is possible to compare not only alternative treatment options for the same disease, but also treatment options between different diseases. This may prevent the unlimited increase of healthcare costs by comparing the cost-effectiveness of a treatment with a local cost-effectiveness threshold. In previous studies it has been shown that cost-effectiveness analyses of child and adolescent mental health problems are often still lacking and more knowledge is needed. Currently, it seems that pharmacotherapies in ADHD are cost-effective compared to no treatment and to behavioral therapies. As stated in the previous section, adherence can be of influence on the outcome of the treatment. In chapter 4 the cost-effectiveness has been evaluated from a societal perspective of a switch from short-acting methylphenidate to long-acting methylphenidate in children who are sub-optimally treated. The switch of medication type was deemed cost-effective because of the possible improvement of adherence. An effective treatment could not only benefit the patients’ health but also reduce indirect costs in healthcare and productivity loss of family members.

In summary, although often highly effective in the treatment of (short-term) behavioral problems in children, more factors need to be considered when looking at the effectiveness
of psychotropic medication like methylphenidate. Like all drugs, it should be questioned to what extent the efficacy, established in controlled trial settings, hold outside formal trials. This is especially true for long-term effects and complex outcomes like school performance. In addition, it is important to also consider the negative (long-term) effects of drug use, like growth retardation.

In the first chapters of this thesis the use of methylphenidate was assessed, related to the real life outcomes of school performance, treatment adherence and persistence, and cost-effectiveness of treatment. All three studies have shown that there are opportunities for improvement in the treatment with methylphenidate. In school performance related to methylphenidate use the early starters of methylphenidate treatment are lagging behind compared to their peers when it comes to academic performance. When it comes to treatment adherence of methylphenidate, comorbid atopic diseases increase the risk of treatment non-persistence in children with ADHD. Our cost-effectiveness analysis showed that it could be cost-effective to switch children with adherence problems from short-acting to long-acting methylphenidate.

In the next chapters the association between atopic diseases and ADHD will be discussed in both children and adults, and the possibilities for treatment improvement.

WHAT IS THE ASSOCIATION BETWEEN ATOPY AND ADHD IN CHILDREN AND IN ADULTS?

The uncertain effects of long-term use of ADHD medication and the related improvements of functional limitations, together with the non-curing effect of ADHD medication has triggered a scientific and societal discussion regarding the treatment of ADHD. Current treatment strategies are mainly focused on coping with symptoms of ADHD. The possibilities of early intervention or even the prevention of ADHD is being discussed as a possible future alternative for treatment of ADHD later in life. Targeting the possible causal pathway that leads to ADHD could reduce the burden of the disorder, the associated impairment on the long term and the possible need for future treatment. However, currently the etiology and pathophysiology of ADHD are still largely unclear. Therefore, research is needed into high risk and negative outcome predictors of ADHD, ADHD treatment strategies for early intervention of atypical neurodevelopment in preschool children and strategies to reach the specific target group of children at high risk for developing ADHD before early intervention could make a possible contribution in the care and cure of ADHD.

Psychiatric disorders are defined by a set of symptoms associated with clinically significant impairment of functioning, and may affect cognition, emotion regulation, or behavior. The distinction between psychiatric disorders and physical diseases is mainly a practical consideration based on which medical discipline is primarily responsible for the treatment. The DSM defines a mental health disorder as described in box 1. However, the classification and
definition of psychiatric disorders have been discussed for over 150 years and still a consensus has not been reached.29 A reason for the expressed doubts regarding the validity of psychiatric disorders is the high level of heterogeneity of psychiatric disorders, caused by a lack of a clear biological defect. Rather, psychiatric disorders have a multifactorial etiology, leading to differing patterns of symptoms and severity and varying effectiveness of treatment strategies.29,30 This heterogeneity of psychiatric disorders makes that diagnosis, treatment, and research into psychiatric disorders need to take a different approach compared to the study of most somatic diseases, e.g., where there is often a clearer distinction between disease and health.

**Box 1. Definition of a mental health disorder by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.**

“A mental disorder is a syndrome characterized by clinically significant disturbance in an individual’s cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress or disability in social, occupational, or other important activities. An expectable or culturally approved response to a common stressor or loss, such as the death of a loved one, is not a mental disorder. Socially deviant behavior (e.g., political, religious, or sexual) and conflicts that are primarily between the individual and society are not mental disorders unless the deviance or conflict results from a dysfunction in the individual, as described above.” - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

**Atopy and ADHD in children**

In 2010 Schmitt et al.31 reviewed the available evidence regarding the possible association of atopic diseases, like asthma, eczema, and rhinitis, and ADHD. The authors concluded that although it appeared that eczema was independently associated with ADHD, and not atopy in general, the quality of studies was low and conclusions about causality were impossible to make. The study in chapter 4 showed that besides an association between eczema and ADHD, it is also likely that there is an independent association between ADHD and asthma and rhinitis. In addition, we showed that parental medication use for asthma and allergic rhinitis was associated with ADHD medication in the child. These findings suggest a possible genetic link or a shared environmental component in the association between atopy and ADHD. Alternatively, increased healthcare-seeking behavior could be underlying the association between the diseases, in which being treated for one disease makes it more likely that a second disease is also noticed. However, our whole study population is to a greater or lesser extent exposed to healthcare, which makes healthcare-seeking behavior a less likely explanation, especially in the association between parental atopy and ADHD in the child. Moreover, studies have shown an association between asthma, rhinitis, and ADHD independent of treatment.32,33
The study in chapter 5 showed that individuals with atopic disease have greater chance of developing ADHD later in life compared with persons without these diseases. A recent meta-analysis confirmed the strength of this association between atopic diseases and ADHD with similar results. (Miyazaki et al. 2017) The underlying mechanism behind the association is still unclear. The lack of studies measuring ADHD symptoms at baseline shows that both an association in co-occurrence or an association in atopy preceding ADHD could exist; atopy before the occurrence of ADHD is a predictor for atopy later in life and vice versa. The lack of baseline correction of ADHD symptoms is also the base for the poor study quality rating addressed in both meta-analysis.

To test the association in a real-life setting we performed a time-series analysis in chapter 7 to address the possible causal pathway between atopic diseases and ADHD. The objective was to determine the temporal order of the co-occurring association between symptoms of atopic disease and ADHD on an individual patient level. Although time-series analysis has the potential to be a useful method to assess the temporal order of the association between atopy and ADHD, no consistent order was observed within our study population. Nevertheless, chapter 7 provided additional evidence that the symptom expression of atopy and ADHD are related.

Pathophysiology of the association between atopy and ADHD
Multiple pathophysiological mechanisms have been raised to explain the possible comorbidity between ADHD and atopic diseases. Three main biological models have been proposed which could explain the possible relation between ADHD and atopic diseases.34 The first model proposes that the chronic inflammation caused by the allergic reaction can expose the developing brain of a child to both high levels of inflammatory cytokines and to early life stress.34 For example, the ability of inflammatory cytokines to cross the blood-brain barrier allows to potentially interfere with cognitive and behavioral development.35 Also, both stress and cytokine release have been found to play a crucial role in the development of specific brain regions that control functions like attention, motivation, and cognition. Changes in the development of these specific brain regions can increase the chances of developing ADHD. The second model proposes an alternative direction of the possible association between ADHD and atopic diseases, in which an increased level of stress related to ADHD is the base for neuroendocrine processes related to the onset of allergic inflammation.34 Sleep problems as an effect modifier or mediator of the association between atopy and ADHD has been of special interest.36,37 Although sleep is essential for the maturation of the brain, and atopy is known for affecting sleep quality, associations between atopy and ADHD independent of sleep have been shown.35 In chapter 7 even an association was observed between sleep problems and decreased ADHD symptoms.

The last model proposes involvement of shared risk factors, like genetic predisposition38, or perinatal problems which could lead to both disorders.34 Since neurodevelopmental disorders like ADHD are likely to be caused by an interplay of multiple factors, i.e., genetics, epigenetics,
biological, psychosocial, and other environmental factors, the three proposed models do not have to be mutually exclusive and could reinforce each other.\textsuperscript{39}

An alternative hypothesis, fueled by the effect of the hypoallergenic restricted elimination diet in children with ADHD, suggests that ADHD itself is a hypersensitivity reaction in some individuals.\textsuperscript{40,41} Multiple studies found a significant positive effect of diet on ADHD related symptoms. However, a review of the studies found significant methodologic shortcomings and labeled the effect of diet as uncertain.\textsuperscript{42} Future randomized and double-blind trials into the effects of the treatment with the restricted elimination diet could indicate the added value of this diet over current treatment strategies. Despite results indicating that it is more likely that ADHD is a non-allergic hypersensitivity reaction these cannot rule out the possible involvement of allergic mediated mechanisms.\textsuperscript{41} For example, the histaminergic system has a central role in the allergic process, but is also involved in the neurotransmitter pathways involved with ADHD.\textsuperscript{40} The multifactorial etiology of ADHD and the co-occurrence of both allergic and non-allergic hypersensitivity complicate the determination of a possible mechanism of action behind the possible association between ADHD and atopic diseases.

A recent hypothesis of the pathophysiology behind the association between atopy and ADHD was fueled by results of a small randomize, double-blind, placebo-controlled crossover study in which 38 children diagnosed with comorbid ADHD and allergy were exposed to cetirizine, methylphenidate, or a combination of both.\textsuperscript{43} Measurements of serum nerve growth factor (NGF) levels were done to assess the possible involvement of NGF and the interaction between the immune and the nervous system. NGF could accommodate the association between ADHD and atopy by regulating immunoglobulin production, essential for an allergic response, and playing a major role in the regulation of the allergic inflammatory response, which is critical in the interaction between the nervous and immune system, but also to the endocrine system.\textsuperscript{43}

The majority of the hypotheses raised for the pathophysiological mechanism behind the association between atopy and ADHD remain speculative. However, the results collected in both chapter 5, chapter 6 and chapter 7, together with the results of Yang et al. (2016)\textsuperscript{44}, could point in a specific direction. A link in the co-occurring of both atopic diseases and ADHD, with the possibility of the atopic disease being of influence on the symptoms or symptom expression of ADHD. Since ADHD has a subjective nature and the assessment of ADHD symptoms in both the study of Yang et al. (2016)\textsuperscript{44} and chapter 7 were done using subjective measurement methods it is difficult to determine if atopy is influencing the disorder or symptoms itself, the burden of the symptoms or just the subjective perception of the disorder. To unravel to complex pathophysiological mechanism behind the association between atopic diseases and ADHD, prospective and longitudinal study-designs with multiple measurements of atopic and ADHD symptoms are needed.
Atopy and ADHD in adults

In the previous sections we have shown that an association between atopy and ADHD is present in children. However, whether the association is also present in adults is still unclear. Over the last years there seems to have been an increase in diagnosis of ADHD in the adult population.45 However, good quality epidemiological studies into the prevalence of adult ADHD is limited.46 About two-thirds of the children with ADHD continue to have problem into adulthood.47 Recently, however, interest has gained in the adult onset ADHD.48 A recent report by the Dutch pharmacovigilance center Lareb reviewed adverse drug events of methylphenidate in the adult population. Because of an uncertain risk-benefit ratio methylphenidate is not registered for the use in adults.49 Based on the reports of adverse drug events submitted to the Lareb, in which the majority of the adverse events were either cardiovascular or psychiatric adverse drug reactions, Lareb advises to monitor the effects and adverse events of ADHD medications in daily practice. Therefore, it is recommended for future studies to describe the extent of ADHD medication use in the adult population is using medication for the treatment of ADHD was however not clear. In chapter 8 we assessed the increased prevalence incidence trends of methylphenidate use in adults. Taken into account the results of chapter 5, 6, and 7 concerning the association between atopy and ADHD in children, looking into the association in adults could benefit and clarify the increase in medication use in adults with ADHD. However, the association between asthma and ADHD appears to be stronger in adults compared to children. Because pharmaceutical treatment of adults with ADHD is on an off-label base it could be that selecting adult patient based on methylphenidate use is resulting in more severe ADHD. This could have caused the stronger association between asthma and ADHD, but does not explain the similar strength of the association between rhinitis, eczema and ADHD in both children and adults. Although, the underlying mechanism of the association in adults is also not clear, similar studies also found a co-occurrence of both diseases comparable to the association in children.50

As the diagnosis of ADHD and the related medication use in adults seems to increase, evidence indicates an association between atopic diseases and ADHD, similar or even stronger compared to the association in children.

Evaluation of causality

To evaluate the possible causal link between atopy and ADHD the Bradford Hill criteria for causation are very useful.51 Although not a checklist, the list of criteria does give an idea about the possible causal link between two biological parameters. The first criteria are the strength and consistency of the association. In chapter 6 we showed that children with an atopic disease have over higher odds of having ADHD later in life, compared to controls. A second meta-analysis considered the association between asthma and ADHD to be even higher at 80%.38 The results of the association between atopy overall and ADHD in both meta-analyses is considered to be weak to moderate. However, both meta-analyses show a consistent association under different study conditions. Although
a strong association is considered to be more likely to be causal because of the possibility of (unmeasured) confounding this does not mean that causality should be ruled out because of the observation of a weak association. Moreover, studies have found a severity-response association\textsuperscript{52} and a duration-response association\textsuperscript{53}.

The next criterion is the specificity of the association, in which an exposure is more likely to be causal if it is associated with a specific disease, rather than multiple outcomes. In chapters 5, 6 and 7 we have shown that atopy is linked to ADHD, however, similar studies have also found an association between atopy and autism.\textsuperscript{54-56} This indicates that the association between atopy and ADHD is not considered specific. However, as stated before, psychiatric disorders like ADHD have a high level of heterogeneity, and are usually caused by a lack of a clear biological defect. As a result, psychiatric comorbidities could therefore be a consequence of the classification system, and not primarily pointing to the existence of separate disorders, as discussed in the introduction of this thesis. This leaves the possibility open for a specific association between atopy and a biological problem leading to ADHD and possibly other (neurodevelopmental) mental health problems, of which the mechanism is not yet understood.

Another criterion is the temporality of the association, which is established when the exposure precedes the outcome. The fact that atopic manifestations often exceed ADHD naturally, because assessing ADHD in early childhood is difficult, makes the assessment of temporality complex.\textsuperscript{57} Chapter 7 gave insight into the temporal order of the association between atopy and ADHD, but showed a difference in direction of the association within our study population.

The last criterion is the biological plausibility of the association. Although not scientifically proven, there are multiple hypotheses about the biological origin of the association between atopy and ADHD, which are described in the previous section.

Overall, we cannot conclude that there is a causal link between atopic diseases and ADHD on a group-based level.

**Clinical implications**

Although the mechanism behind the association between atopy and ADHD is not clear, the association may have clinical relevance. New insights into underlying mechanism could not only improve the care of both diseases but can also lead to new views on pathogenesis and treatment of both diseases. A large proportion of patients with atopy face undertreatment and underdiagnosing because of low recognition and acknowledgement.\textsuperscript{58} Greater awareness in physicians of increased atopic symptoms in children with ADHD could deal with these issues in diagnosis and treatment of atopic diseases.

A recent study, considering the effects of treatment of allergic rhinitis on ADHD symptoms supports our findings that there could be a direct link between symptom expression of atopy and symptom expression of ADHD.\textsuperscript{59} The study showed that ADHD scores improved with the treatment and decreasing symptoms of rhinitis. Furthermore, having multiple atopic diseases was a predictor for the improvement of ADHD when being treated for rhinitis. In a second study in which children with comorbid allergic rhinitis and ADHD were treated with
either an antihistamine, a stimulant, or a combination of both, a benefit was shown when being treated with the combinational therapy. An enhancement of both treatment efficacies in reducing symptoms of the diseases suggest a synergistic effect, in which stimulants have a antihistaminic effect and antihistamines have an anti-inflammatory effect and reduce ADHD symptoms. This could potentially reduce dosage of both treatments. Interventions of comorbid ADHD and atopy should be explored in which collaboration between care disciplines is essential. For example, the screening for atopy during ADHD diagnosis could be a strategy to explore further in the treatment of ADHD. It has been shown that a treatable comorbid somatic disorder in an individual is masking as a psychiatric disorder. For example, metabolic screening of individuals with psychosis revealed a significant amount of new treatment options. Interdisciplinary awareness of associations between psychiatric disorders, like ADHD, and somatic diseases, like atopy, has the potential to improve care in both children and adults. Thoughtfully planning of ADHD management by the physician in patients with comorbid atopic disease is an example of which both less costs and better treatment can be established. Especially in disorders with complex etiology and heterogeneity of treatment effectiveness, prioritizing the control or even cure of somatic symptoms and comorbidities should be explored.

In summary, ADHD and atopy are both prevalent diseases in which symptoms both co-occur and precede each other. Whether the symptoms of both disorders are part of one disease pattern or as separate psychiatric and somatic disorder is unclear. Both in children and adults, an association between both conditions is likely to be a direct link between both conditions. Data suggest that treatment of either ADHD or atopy can benefit the other disease. Because atopy is generally a treatable disease but not always acknowledged and recognized, the assessment of an atopic disease in the diagnosis of ADHD should be explored as part of future care of ADHD.

GENERAL CONCLUSION

In the first part of this thesis we have looked at the use of methylphenidate and considered real life outcomes of school performance, treatment adherence, and cost-effectiveness of treatment, to assess the impact of psychotropic drug use in children with ADHD. Based on our findings we do not only show the need for the improvement of treatment with methylphenidate related to a diverse range of outcomes, but also show the potential to improve treatment with methylphenidate. In second part of this thesis we zoomed in on the association between atopic diseases and ADHD, to see if there is an association between both diseases in children and adults. Although the underlying mechanism of the association between atopy and ADHD is not clear, the association is present in both children and adults. Thus, more knowledge is needed concerning the underlying mechanism of the association between atopy and ADHD. For clinical practice the association between atopy and ADHD...
could have the potential to contribute to the improvement of care for individuals with either atopy or ADHD. The first step will be to increase the awareness of physician treating either children or adults with ADHD or atopic diseases. The second step could be that a better recognition and acknowledgement of atopic diseases in the diagnosis of ADHD could already have the potential to improve care by tailor fitting treatment to the individual. Because atopy is a treatable and even curable disease the presence of an atopic diseases should be addressed in the diagnostic process of ADHD and vice versa. In addition, the monitoring of medication use in individuals with both comorbid ADHD and atopy could have the potential to improve adherence problems and improve treatment outcome.
REFERENCES


