Comorbidities, complications and treatment of childhood obesity

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Section 5

Conclusions and perspectives

Chapter 9

Conclusions and perspectives on comorbidities, complications and treatment of childhood obesity

SUMMARY, CONCLUSIONS AND PERSPECTIVES

Summary and conclusions

Childhood obesity has become a major health issue worldwide due to the rising prevalence, increase in frequency of morbid obesity, and the knowledge that up to 80% of the children with obesity become adults with obesity [1-3]. Obesity has been associated with common pediatric diseases such as asthma, attention-deficit/hyperactivity disorder (ADHD), fatigue, constipation, and vitamin D deficiency [4-8]. However it is unclear whether the diagnosis and treatment of these diseases is influenced by obesity. In addition, screening on complications of obesity in children is frequently debated as risk factors are not completely clear and best screenings methods not known. Furthermore, treatment of childhood obesity with lifestyle intervention is often associated with minor weight loss only, and studies into additional therapies with pharmacological agents are often limited by a short follow-up period.

Therefore, the studies described in these thesis aimed to contribute to the treatment of comorbidity in children with obesity, screening for the complications of obesity, and treatment of childhood obesity.

In **Section I** of this thesis on comorbidities in childhood obesity, the common pediatric diseases asthma and ADHD were studied in children diagnosed with obesity. For asthma in children with obesity, the diagnosis asthma was evaluated based on clinical parameters and/or spirometry results, ultimately to evaluate overtreatment with asthma medication in this population. For ADHD, we evaluated the influence of (the dose of) psychostimulants on body mass index standard deviation score (BMI-SDS) and height-SDS in a pediatric cohort with ADHD from an outpatient clinic.

Asthma is frequently observed in children with obesity [9]. It has even been suggested that the risk on developing asthmatic symptoms increases with BMI [10]. In addition, the response to asthma medications might be influenced by BMI, since some patients demonstrate asthmatic symptoms which are more difficult-to-control with increasing BMI [4,8]. Several causes have been postulated to understand the association between asthma and obesity and the difference in response to medication, of which overdiagnosis is nowadays increasingly suggested as cause [11-15]. Therefore in **Chapter 2**, it was investigated whether the diagnosis asthma in children with overweight/obesity and "asthmatic symptoms" was preceded by a diagnostic process as recommended in the guidelines. Thereafter the percentage of over- and undertreatment of asthma was studied. In this study in children with overweight/obesity, a child was considered as having "asthmatic symptoms" if β2-agonist and/or inhalation corticosteroids (ICS) were used and/or diagnosis asthma was recorded in the medical file (n=338), which was retrospectively reassessed based on clinical symptoms and spirometry results reported in medical files. Children were classified in no, unlikely, probable, and confirmed asthma.

Overtreatment was defined as asthma medication use in participants classified as no or unlikely asthma and undertreatment as probable or confirmed asthma without asthma medication use. Results showed that more than 25% of children with overweight/obesity and "asthmatic symptoms" did not meet the criteria for asthma and were consequently overtreated according to the used definition. This result emphasizes the necessity for a standardized evaluation of asthmatic symptoms in children with obesity using questionnaires and lung function tests before treatment start, as well as the need for regular reassessments of symptoms and consequently indication for treatment. However, it should be noted that undertreatment was observed in nine (2.7%) participants as well, which could even be more harmful, since this might increase the risk on asthma exacerbations, decrease quality of life, and contribute to the development of overweight/obesity as asthmatic symptoms might interfere with exercise capacity. In conclusion, the diagnosis asthma children with overweight/obesity should be carefully weighed to minimize both over- and undertreatment.

ADHD is another frequently observed comorbidity in children with obesity [7]. ADHD is characterized by a pattern of inattention, hyperactivity, and impulsivity with an early onset in life [16]. It is often treated with psychostimulants which are associated with weight loss and growth retardation due to their known negative effect on appetite [17-21]. Due to the hyperactivity and associated side-effects of psychostimulants, ADHD is often associated with underweight. However, recently a 40% higher prevalence of obesity in children/adolescents with ADHD compared to normal weight counterparts was reported [7]. Therefore, in **Chapter 3** the effect of psychostimulants on weight and height in children with ADHD stratified by BMI-categories was evaluated. In addition, the association between the dosage of the psychostimulant and weight and height changes was studied. For this, the change in BMI-SDS and height-SDS of 298 children with ADHD stratified into different BMI-categories (median age 9.8 years, height-SDS 0.0, BMI-SDS 0.5, psychostimulant dosage 0.5 (0.2 to 1.4) mg/kg/day) was evaluated over a follow-up period of 18 months. The results show small but significant BMI-SDS reductions in all BMI-categories except in the underweight subgroup, even though in the latter the highest psychostimulant dosage per kg/day was used. The observed growth retardation was also small but significant and was shown in all BMI-categories except the overweight subgroup. Psychostimulant dosage was only weakly correlated with a change in BMI-SDS ($r= -0.3$ (-0.9 to +0.5); $p<0.01$) and height-SDS ($r=-0.2$ (-0.4 to -0.1); $p=0.01$). These results raise the question whether weight reduction and growth retardation are induced by the side effects of psychostimulants on appetite or whether this has another origin. More specifically, it has been suggested that BMI might be a reflection of the variability of ADHD symptoms since inattentive and impulsive components of ADHD could lead to inactivity and irregular and dysregulated eating patterns resulting in a higher risk of overweight/obesity [7,22-24]. As a consequence, reductions in BMI might

be related to a reduction of ADHD symptoms due to adequate treatment, rather than a side effect of psychostimulants. As such, it can be hypothesized that overweight/obesity in children with ADHD might be related to insufficient treatment of ADHD symptoms. In conclusion, after 18 months of psychostimulant treatment, a significant decline in BMI-SDS and height-SDS was observed. However, the correlation with psychostimulant dosage was weak, and the decline was not observed in all subgroups. Therefore, further studies on the aetiology of BMI-change are warranted, particularly with regard to the ADHD symptoms.

In **Section II** on the complications of obesity we focused on metabolic- and cardiovascular complications of obesity. Insulin resistance (IR) is usually the first sign of a disturbed glucose metabolism and therefore considered as a precursor of type 2 diabetes mellitus (T2DM) [25,26]. IR is also recognized as independent risk factor for development of cardiovascular diseases [27,28], and is associated with the metabolic syndrome [28]. Due to the association with complications, it is of great importance to early identify those at risk for IR development. Multiple risk factors for IR development have been suggested, though there is no consistency yet on which factors are contributing the most [29-32]. In addition, it has been suggested that there might be differences in risk factors between children and adolescents [29-32]. Therefore, in **Chapter 4** a retrospective analysis into potential risk factors for IR development in children/adolescents with obesity was performed, stratified for children (< 10 years) and adolescents (≥10 years). In total 777 patients with obesity visiting a pediatric (obesity) outpatient clinic were studied. Insulin resistance was defined as a Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) ≥ 3.4 [33]. Of the 306 children 51 (16.7%) and 38 (12.4%) children were diagnosed with IR and metabolic syndrome, and of the 471 adolescents 223 (47.3%) and 95 (20.2%), respectively. Different predictors for IR development were observed between children and adolescents. In children BMI-SDS, preterm birth, and Tanner stage were associated with IR development, while in adolescents BMI-SDS and waist circumference were associated with IR. These differences in risk factors for development of IR can be used as a basis to optimize screening in the different pediatric populations.

Besides insulin resistance and T2DM, cardiovascular diseases are a well-known complication of obesity in adults [34]. Since the prevalence of childhood obesity is rising and shifting towards a younger age, and morbid obesity is more frequently observed, cardiovascular diseases are shifting towards a younger age as well [35,36]. Although awareness of childhood cardiovascular risk management is increasing, specific measurements for early cardiovascular changes in children with obesity are rarely performed during routine clinical care, besides the evaluation of the blood pressure and lipid spectrum [36]. This can lead potentially to underestimation and consequently undertreatment of obesity related cardiovascular complications, while it is known that early detection, evaluation, and treatment of cardiovascular changes can result in reversibility of cardiac

abnormalities [36]. Therefore, in chapter 5 and 6 the focus was on different methods of measurements to detect early cardiovascular changes in children/adolescents. Hence, children/adolescents with and without obesity were compared for cardiovascular changes.

In **Chapter 5**, arterial stiffness, an early sign of atherosclerosis [37-39], was measured with pulse wave velocity (PWV), and augmentation index (AIx) using applanation tonometry in 62 adolescents with obesity and compared with 61 lean controls. In addition, the influence of pubertal stage and IR on arterial stiffness was evaluated. Adolescents with obesity had a higher PWV compared to lean controls, implying increased arterial stiffness. This observation seems even more relevant since the lean controls were older than the adolescents with obesity (15.0 vs. 13.4 years; p=0.01), while it is known that arterial stiffness increases (physiologically) with age [40]. Stage of puberty did not influence arterial stiffness, which is in contrast with the suggestion that sex steroids influence arterial stiffness, especially androgens [41]. In adolescents with obesity and IR, AIx was significant higher compared to adolescents with obesity without IR, implying an additional increase in arterial stiffness in this population. These results suggest that measurement of AS could be considered in adolescents with obesity and particularly in adolescents with IR as part of cardiovascular risk assessment.

Despite the fact that applanation tonometry is considered the gold standard for measuring PWV and AIx, it is questionable whether this should be the preferred method of measurement. Applanation tonometry can be difficult to perform in patients with obesity [42]. In addition, applanation tonometry requires a skilled operator which makes it less suitable in daily clinical practice [42]. Furthermore, since central measurements of PWV from carotid to femoral artery are preferred as this has the strongest correlation with cardiovascular morbidity and mortality, the patient has to be undressed to be able to place the femoral probe which could be uncomfortable and generate resistance and shame especially in adolescents [43,44]. Therefore, in **Chapter 6** we studied a non-invasive method of measuring the development of cardiovascular changes i.e., accumulation of advanced glycation endproducts (AGEs). AGEs are formed endogenously in a non-enzymatic glycation reaction, in which glucose binds irreversible to proteins or lipids [45]. AGEs increase physiologically with age, while they increases more rapidly in the presence of hyperglycemia and oxidative stress [46,47]. Since obesity is associated with increased oxidative stress it has been suggested that AGEs are increased in patients with obesity [48]. AGEs are assumed to play a role in the development of cardiometabolic complications through the modification of the structure, function, and mechanical properties of several tissues including blood vessels [49]. Since some AGEs exhibit fluorescent properties and accumulate in the collagen of the skin, they can be measured non-invasively using skin autofluorescence (sAF) [45,48,50].

We measured AGEs with sAF in 143 children/adolescents with obesity, and compared the results with sAF obtained in 428 lean controls. Stratified by age categories (<10, ≥10–<13, ≥13–<15, ≥15–<17, and ≥17 years of age), significant higher sAF levels were observed in children/adolescents with obesity compared to the lean controls ($p<0.01$), except in those < 10 years of age. Since a significant difference in skin type was observed between children/adolescents with obesity and lean controls in all age categories, an additional analysis stratified by skin type according to the Fitzpatrick scale, which is a classification for human skin color based on skin response to sun exposure, was performed. In this analysis no significant differences were observed in sAF values of children with obesity versus lean controls, suggesting that skin type is a confounder. Therefore, a multivariate analysis was performed which showed that obesity was a determinant of sAF after adjustment for skin type, age, and gender. These results indicate that obesity contributes to increased accumulation of AGEs. These results should be considered in view of a report suggesting that the increase in sAF depends on the duration of obesity and accelerates with longer existing obesity and subsequent development of complications [47,51-53]. This might indicate that AGEs are useful as long-term marker of early cardiovascular disease, while it may not be the best screenings method to detect early changes at a young age with still limited duration of obesity. However, before any clear statements can be made, additional research have to be performed in this young population with obesity in which participants should be matched on skin type and age.

In **Section III** we report on the treatment of childhood obesity. Lifestyle intervention is the cornerstone of the treatment of (childhood) obesity [54]. The main goal of obesity treatment is reduction of weight and thereby delaying or preventing the development of complications of obesity [54]. However, the efficacy of (intensive) lifestyle intervention is often disappointing and long-term effects with respect to maintenance of weight loss are questionable [54,55]. As a consequence, there is an ongoing search for additional (pharmacological) therapies alongside lifestyle intervention, especially for those already diagnosed with complications such as IR [56,57]. Metformin, a biguanide registered for the treatment of T2DM from 10 years of age onwards, is nowadays increasingly used off-label for the treatment of obesity [58]. In children/adolescents, the efficacy of metformin with respect to weight/BMI reduction has been mainly studied on the short term i.e., ≤ 6 months of treatment, showing a BMI reduction between -0.82 and -2.02 kg/m^2 [59,60].

Knowing that there is only a limited number of studies on the efficacy of metformin of >6 months in children with obesity, we studied and evaluated in the third section of this thesis the efficacy of long-term metformin treatment. For this, a literature review and an open label extension study were performed. First, the results of a systematic review on long-term efficacy of metformin treatment with respect to weight reduction and progression towards T2DM in children and adults with obesity are presented in **Chapter 7**.

In total 29 studies (15 pediatric and 14 adult studies) were identified. In children, the intervention period ranged between 6 and 36 months, with 6 studies having an intervention period > 6 months. For the twelve studies reporting on BMI changes after 6 months of treatment, BMI was found to change between -2.4 and +0.02kg/m^2 in those receiving metformin and between -1.1 and +0.9 kg/m^2 in controls. In 8 out of 12 studies reporting BMI after 6 months of treatment a significant greater reduction in BMI was observed in the metformin versus the control group. In the 6 studies with an intervention period of > 6 months, in general no additional improvement of BMI was observed after 6 to 9 months of treatment. However, BMI was significantly lower in the metformin versus the placebo group at study end after 12-18 months of treatment [61-64]. In 3 studies, a larger improvement in insulin sensitivity was observed in the metformin versus the control group. Prescribed metformin dosages differed between studies and varied between 1000 and 2000mg per day. The dosage that was used seems to influence the efficacy with respect to BMI reduction as 9 out of11 studies prescribing ≥ 1500mg metformin per day showed a significant decrease in BMI, while this was the case for only 2 out of 4 studies prescribing 1000mg a day.

In the 14 adult studies, intervention period ranged between 6 months and 15 years, of which 10 had an intervention period of more than 6 months. In general, small decreases in weight/BMI (weight: -5.8kg to -0.9kg and BMI: -1.4 to -0.4kg/m^2) were observed and maintained irrespectively of duration of metformin intervention, while in controls weight/BMI in some studies decreased and in others increased (weight: -2.3 to +1.4kg; BMI: -0.6 to +0.5kg/m^2). In 11 out of 14 studies, a more profound decrease in weight/BMI was found in the metformin versus the placebo group ($p<0.05$). In addition, in all of the 7 studies reporting on progression towards T2DM, the incidence of T2DM was lower in the metformin group, with a risk reduction between 7 and 31% compared to placebo or standard care [65-71]. No clear association between metformin dosage and weight/BMI reduction was observed in the adult studies as in 4 out of 7 studies prescribing ≤ 1000mg metformin as well as in 4 out of 7 studies prescribing ≥ 1700mg metformin a decrease in weight/BMI was observed in the metformin versus the control group ($p<0.05$). In summary, in children using metformin the maximum reduction in BMI was observed after 6-9 months of treatment, but they still had a significantly lower BMI compared to controls after 12-18 months of treatment. In adults weight/BMI reductions were more pronounced than in children and maintained irrespectively of duration of treatment. In addition, a significant reduction in the progression toward T2DM was observed in adults using metformin. Therefore, metformin should be considered as a treatment for obesity and its related complications in both children and adults.

In **Chapter 8**, the results of an extension study of 18 months open label metformin treatment in children with obesity and insulin resistance who previously participated in a 18 months randomized controlled trial on the long-term efficacy and safety of metfor-

min are presented. Thirty-one of the 42 included participants completed the extension study (74% girls, median age 14.8 (11.6 to 17.9 years), BMI 31.2 (22.3 to 45.1 kg/m^2), HOMA-IR 3.4 (0.2 to 8.8)). At start 22/42 (52.4%) participants were eligible for metformin of which 13 (59.0%) agreed with treatment. In participants who used metformin for 36 months (those who started metformin treatment in the RCT and continued metformin treatment in the open label extension study), an increase in median BMI (+2.2 (+0.2 to +9.0 kg/m^2)) and median HOMA-IR (+13.7 (+1.6 to +48.3)) compared to the start of the open label extension study was observed. In metformin naïve participants who used metformin for 18 months (those who received placebo in the RCT and started metformin treatment in the open label extension study) median BMI initially decreased during the first 6-9 months of treatment but stabilized at 18 months at +0.5 (-2.1 to +5.1 kg/m^2)). For HOMA-IR a median decrease was observed (-1.1 (-4.6 to +1.4)). In summary, while metformin treatment in metformin naïve participants seems to result in an initial decreases in BMI and HOMA-IR, there is no evidence for sustained effect after prolonged use in adolescents based on the current study.

Perspectives

The importance of the diagnostic process for optimal treatment of common pediatric disorders in children with obesity.

In **Section I** of this thesis it has become apparent that there should be extra attention for the diagnostic process and optimal treatment of common pediatric disorders when they occur in children with obesity. Accurate diagnosis of diseases is important in general, as there are obvious consequences associated with erroneous diagnosis of diseases [13,72]. This includes the lost opportunity to treat the origin of complaints and the potential exposure to adverse drug effects, but also increased health care cost due to (not indicated) medication use or supportive treatment, the social and psychological impact of being labeled with a (chronic) disease, and as a result of all previous mentioned issues a decreased quality of life [13,72]. In children with obesity this might be even of more importance as they are supposed to have an increased risk for a decreased quality of life [73].

Standardized assessment of symptoms together with the required diagnostic tests to confirm the diagnosis are therefore of great importance, even though they should be individualized when necessary. In addition, regular evaluation of diagnosis and indication for therapy should be performed to minimize the risk on under- and overtreatment. This seems especially of importance in children with obesity, in which symptoms of diseases might be caused by the actual disease but also be a result of obesity. This has been shown in chapter 2, in which "respiratory symptoms" were frequently labeled as asthma with subsequent treatment, while the criteria for the actual diagnosis asthma were not

met. Symptoms might have been caused by a poor condition related to overweight/obesity and/or caused by an enhanced perception of nonspecific symptoms such as dyspnea, resulting in overtreatment with asthma medication [13,74].

Besides accurate diagnosis of diseases, adequate treatment is of great importance as well. In general, drugs can be dosed on weight (mg/kg/day), (plasma) concentrations (Therapeutic Drug Monitoring), laboratory values, and/or symptoms. In children most drugs are prescribed based on weight and since they are growing, dosages are regularly assessed. In case children with overweight/obesity are dosed based on weight, their dosage is relatively high compared to children of the same age with a healthy weight. An important question in this respect is therefore whether dosages in children with obesity should indeed be based on total body weight or whether dose capping or dose adjustments to for instance lean bodyweight should be applied. Another approach would be to use the adult dosage for children/adolescents with obesity, which has been proposed for instance for metformin because of increased clearance in children with obesity compared to children without obesity [75]. From the literature, it is known that obesity may have an impact on drug pharmacokinetics, as obesity may result in changes in tissue composition, increased circulating blood volume and cardiac output, and altered liver and kidney function [76]. For midazolam for instance, an even higher clearance and therefore dose for adolescents with obesity was identified compared to adults with obesity [77]. As such, it seems that drug dosages in children/adolescents with obesity should be individually adjusted thereby taking the pharmacokinetic changes due to excess of weight into account, as for many drugs there are no specific guidelines for dosing in obese children yet.

The results of chapter 3 show that for ADHD, children with obesity received the lowest median mg/kg daily dosage of psychostimulants compared to the other BMI-categories, which may imply that these children are underdosed [78]. On the other hand, these drugs should primarily be titrated based on symptoms and therefore the dose expressed per kg can not imply underdosing by itself. Furthermore, it should be noticed that many drugs are available in fixed tablets only, which limits the possibility to vary with dosages with a risk of both under- or overdosing. Possibly, pediatricians treating children with obesity with ADHD are reluctant to increase the dose any further because of fear of side effects[78]. In contrast, other studies suggest that the negative effect of psychostimulants on height is rather small and attenuates over time and is therefore not of clinical significance [78-83]. Considering the observations in our study and in the literature, concerns regarding negative effects of psychostimulants on both weight and height can be waived, and should not be a reason to priori reduce the dose in subjects with obesity.

Adequate treatment in children/adolescents with ADHD seems to be of particular importance, since it has been suggested that overweight/obesity might be caused by

(over)expression of specific ADHD symptoms [7,22-24]. It has been hypothesized that inadequate treatment of ADHD can result in weight gain and thereby increase the risk on development of obesity related complications. Therefore, it is of importance to scrupulously register ADHD symptoms before treatment and to evaluate these symptoms regularly during treatment to titrate the dosage on symptoms. In order to do so, ADHD symptoms scoring lists such as the ADHD-Rating Scale-IV, Swanson Nolan And Pelham IV-list (SNAP IV), and the Clinical Global Impression of Improvement list should be used in daily clinical practice [84]. The use of these scoring lists might be helpful to study the relation between ADHD symptoms and the development of obesity, as well as the influence of obesity on the dosage needed to achieve adequate treatment of ADHD.

The approach used to study asthma and ADHD in children with obesity can also be applied to other common pediatric diseases in children with obesity such as vitamin D deficiency and infectious diseases. The diagnostic procedure should be accurate and reproducible and drugs should be titrated based on a combination of weight and symptoms. To achieve this, it is of great importance to measure the weight regularly and to register symptoms precisely. In addition, pharmacokinetic- and pharmacodynamic studies should be performed in children with obesity to find the most appropriate weight-based dosing strategy. In conclusion, accurate diagnosis of common pediatric diseases in children with obesity and dosing regimens based on pharmacokinetic changes caused by obesity and observed symptoms, will advance optimal treatment in this specific pediatric population.

The importance to screen for cardiometabolic complications in children with obesity

In **Section II** of this thesis risk factors and screenings methods for cardiometabolic complications were discussed. Since obesity is seen at a younger age and morbid obesity is more frequently seen also in children, cardiometabolic complications are nowadays also seen at younger age [54,85,86]. This was demonstrated in chapter 4, in which IR was observed in 17% of the children <10 years of age and in 47% of the adolescents [87], as well as in chapter 5 in which the arterial stiffness was significantly higher in adolescents with obesity compared to lean controls and even more pronounced in those with obesity and IR. These results underline the necessity for screening on obesity related complications in childhood to detect (precursors of) complications and to be able to treat them in a timely manner to prevent progression. As it was shown by our study that there are differences in risk factors between children and adolescents [87], together with the known differences in risk factors between ethnicities [88], more individualized (i.e., age and ethnicity specific) screening on cardiometabolic complications should be applied.

At the moment there is no consensus yet on which screenings method should be used to identify IR, as multiple methods are used concurrently [33,61]. Recently, it has been shown that if HOMA-IR with ≥3.4 as cut-off value is used as screening tool, the majority

of children at risk for T2DM will be identified. Therefore, this seems the preferred method despite the fact that a fasted blood sample is required [33]. With respect to screening on (precursors of) cardiovascular diseases in children with obesity, there seems even less consensus. For an optimal method, early signs of subclinical cardiac dysfunction should be detectable, given the potential for reversibility when treatment is start in a timely manner [36]. Both increased arterial stiffness and increased carotid intima-media thickness (CIMT) are early signs of arthrosclerosis and could therefore be useful in the screening on (precursors of) cardiovascular disease in children [36,89]. Arterial stiffness can be measured using PWV and AIx using applanation tonometry, which is considered the gold standard [42,90,91]. Applanation tonometry requires a skilled operator and can be difficult to perform in subjects with obesity. In addition, since central measurements of PWV from carotid to femoral artery are preferred as this has the strongest correlation with cardiovascular morbidity and mortality, the patient has to be undressed to be able to place the femoral probe which could be uncomfortable and generate resistance and shame especially in pubertal children [43,44]. It is therefore questionable whether this method of measurement is useful in daily clinical practice. The same could be applied for carotid intima-media thickness, as this method required trained staff as well, since it is measured using ultrasound.

From the foregoing it has become clear that assessments of cardiovascular risk into daily clinical practice is challenging and that specialized equipment and/or trained staff is often required. Therefore, the search for a non-invasive and an easy to use screening tool for daily clinical practice in children is ongoing. Chapter 6 showed that AGEs measured with sAF might be such a tool since it is non-invasive, easy to use, and does not require trained staff. However, while obesity was a significant covariate for sAF, no difference in AGEs measured with sAF was noticed between children with and without obesity when stratified by the confounder skin type [92]. It has been suggested that the increase in sAF depends on the duration of obesity and accelerates with longer existing obesity and subsequent development of complications as in adults differences in sAF have been observed between subjects with and without obesity [47,51-53]. This indicates that AGEs might be a useful non-invasive marker of early cardiovascular disease on the long-term, but that due to the relative short duration of obesity in children the value as marker for early cardiovascular changes requires yet further (longitudinal) studies in pediatric populations. These studies should include patients of all ethnicities/skin-types since it is known that skin-type influences AGEs measured with sAF [50,52]. This is of particular relevance, as obesity is more prevalent in ethnic minorities which have more often a darker skin-type compared to Caucasians [93]. Possibly, skin intrinsic fluorescence (SIF), might be a preferred method of measurement instead of sAF since SIF has the possibility of mathematically adjustment for skin pigmentation eliminating skin type as confounder, making it more useful in daily clinical practice [94].

Besides the used screening tool there seems no consensus yet on how often and in which population the screening should be performed. Nowadays most guidelines advise to screen for (precursors of) cardiometabolic complications in children with overweight or obesity only after the onset of puberty or ≥10 years of age, and with one or more additional risk factors for diabetes [88,95]. Risk factors mentioned are (1) maternal history of diabetes or gestational diabetes during the child's gestation; (2) family history of T2DM or cardiometabolic complications in first- or second-degree relatives; (3) race/ethnicity with increased risk; and/or (4) signs of IR or conditions associated with IR.

With respect to the screening interval, it is advised to repeat measurements every 2-3-years and more frequently (i.e., yearly) if BMI is increasing or in case of morbid obesity [88,95]. However, it is questionable whether screening should only be performed in restricted populations i.e., after the onset of puberty or age ≥ 10 years with an additional risk factor, since it has been shown that IR was already frequently observed in children far below the age of 10 years and also in children/adolescents who did not always have an additional risk factor [87]. Moreover, children < 10 years of age have potentially the highest risk for development of complications as they challenge their body already at young age. However, little is known on the actual risk of complications in this young population as they are not often studied. In addition, an important question would be whether a screening interval of 2-3 years does not unnecessarily result into delay of diagnosis and consequently delay of treatment. This seems of particular relevance since it is known that early detection and treatment of cardiovascular complications can result in reversibility [36]. As obesity is shifting towards a younger age and morbid obesity is more frequently observed, it seems reasonable to adjust the currently advised screenings population and interval. In our opinion, screening should be performed in children with obesity at any age (i.e., including children <10 years of age and children without risk factors), and repeated at least once a year or more frequently in case of (severe) abnormalities.

In conclusion it is not evident yet which screening method for cardiometabolic risk factors in children is preferred. The fact that normative data of normal weight children are often scarce or even lacking, also plays a role into this. Therefore, additional studies in children with obesity, preferably within the context of regular care, are necessary to evaluate the progression of cardiometabolic abnormalities and the long-term health consequences. Until new information has become available, screening should be performed in all children with obesity at yearly interval and should include at least the measurement of blood pressure, lipid spectrum, and HOMA-IR.

Metformin as treatment option in children with obesity

In **Section III** of this thesis the efficacy of long-term metformin treatment was evaluated. The efficacy of metformin with respect to weight/BMI change has been mainly studied

on the short term, i.e. ≤ 6 months of treatment [59,60,96,97]. Two meta-analyses have been performed on these studies, reporting a mean reduction in BMI of -1.42 ((95% CI -2.02 to -0.83) kg/m^2 (based on 5 studies) [60] and -1.38 (95% CI -1.93 to -0.82) kg/m^2 (based on 8 studies) [59]. In addition, a recent meta-analysis in studies with an intervention period of 6-12 months of treatment showed a mean reduction in BMI of -0.86 (95% CI -1.44 to -0.29) kg/m^2 (based on 6 studies) [96]. This suggests that metformin could be useful as a pharmacological option in addition to lifestyle intervention in the treatment of childhood obesity. However, in both chapter 7 and 8 it has been shown that the efficacy of metformin with respect to BMI change on the long-term, i.e. > 6 months of treatment, in children is limited, with in general no additional weight loss after 6 to 9 months of treatment [62-64,97-100]. Despite this limitation, the children that used metformin had in general a lower BMI compared to the placebo group at study end (after 12 to 18 months), suggesting a small but beneficial effect of metformin on the long-term [62-64,97,98,100]. In contrast to the studies in children, studies in adults showed that the weight loss achieved under metformin treatment was maintained after an intervention period of 15 years [68,97]. Noteworthy is that the maximum achieved weight loss was observed after 15 years in metformin users [68].

Regarding the efficacy of metformin with respect to the reduction on cardiometabolic complications in children, no clear effect was observed in the extension study nor in reviews [96,97,99]. While these results may be explained by the small number of patients that was included, this result is in sharp contrast with observations made in adults, since a reduction in T2DM incidence between 7 and 31% was observed in those using metformin compared to controls in multiple studies irrespective of duration of intervention [65-71].

On the basis of these results, the question can be raised whether metformin should be considered as a pharmacological option in addition to lifestyle intervention in the treatment of childhood obesity.It is remarkable that there are such great differences in the efficacy of metformin between children and adults with respect to maintaining weight/BMI loss, as well as reduction in progression towards development of complications. It is not entirely clear why the efficacy of metformin differs between children and adults. Differences in compliance to therapy might be one explanation, since it has been shown that weight loss as well as the maintenance of weight loss is strongly associated with compliance to metformin therapy [101,102]. Considering that most studies in children/adolescents are performed in children >10 years of age, pubertal behavior might have influenced compliance to therapy. Compliance to therapy therefore may be greater in adults and as a consequence the efficacy of metformin treatment.

Another explanation for the difference in efficacy of metformin between children and adults is the prescribed daily dosage, which has recently been suggested a determinant of the efficacy of metformin therapy both in our review and other publications[59,97,103].

Clearance of metformin appears to be higher in both children and adults with obesity in comparison with their lean counterparts [75] which raises the question whether the current advised maximum daily dosages of 2000mg/day in children is adequate or should be increased in children with obesity. This seems especially of importance since the prevalence of morbid obesity is rising, which increases the risk of underdosing when prescribing current recommended doses. Since metformin is generally well tolerated and serious adverse effects are rarely seen, it seems that dosages could be increased safely to the currently maximum advised adult dosage of 3000mg/day. However, it should be mentioned that compliance to therapy remains an important determinant of the efficacy of metformin even if the prescribed daily dosage is optimal.

Nowadays, metformin is not (yet) registered as weight loss drug, since an average weight loss of ≥5% which is currently used as criterion to be labeled as weight loss drug was not achieved in any of the studies performed in children or adults [57,97,104-106]. However, despite the fact that the obtained weight loss in children was limited and maximal after 6-9 months of treatment, BMI was still significantly lower compared to controls after 12-18 months of treatment [61-64,100]. Moreover, in adults weight loss was maintained even after 15 years and was almost similar to the weight loss obtained with lifestyle intervention with longer follow-up [68]. In addition, a significant reduction in progression towards development of T2DM was observed in adults, irrespectively of duration of metformin intervention. Taking these results into account, there seems to be a role for metformin in the treatment of obesity and its related complications. Especially since it is known that also improvements in cardiovascular risk factors have been observed after weight loss as small as 3% [57,104,105]. Lifestyle intervention is in general more effective on the short-term with respect to weight reduction and to slow down the progression towards T2DM development, although it has been shown that with longer follow-up the results obtained with metformin become comparable with lifestyle intervention [66-68]. As such, it can be concluded that although metformin does not meet the criteria for being registered as weight loss drug, it can contribute to the treatment of obesity and its related complications, given the obtained weight loss and reduction in progression towards complications. This is of particular relevance because metformin is generally well tolerated and because it has been shown that metformin is cost-saving, while lifestyle intervention is only cost-effective [107]. As a consequence a (major) reduction in health care cost might be achieved with metformin by delaying and maybe even preventing progression towards obesity associated complications [108]. Despite the fact that the efficacy of metformin with respect to reduction in progression towards complications has not yet been observed in children, metformin should be considered as (beneficial) drug in the treatment of pediatric obesity, given the small but favourable effects on weight in this young population and the promising results in adults.

To whom metformin should be prescribed and how long it should be used is not entirely clear yet. Since compliance to therapy is a major determinant of efficacy of metformin, it seems obvious to prescribe metformin only to those that are highly motivated. In addition, it has been suggested that metformin would have a larger impact on weight in subjects with more severe insulin resistance [109]. Therefore, it might be justified to prescribe metformin in those highly insulin resistant, or only in those with impaired glucose tolerance. As demonstrated in the study of the diabetes prevention program research group [68], there seems no extinction of the efficacy of metformin over time with respect to reduction of progression towards development of T2DM and possibly in reducing weight as well. However, it is questionable whether it is desirable to advice to take lifelong medication for this indication. Therefore, it seems more reasonable to evaluate annually the use of metformin based on achieved BMI (< 25 kg/m^2) and /or (absence of) signs of complications such as IR, dyslipidemia, and hypertension.

Ideally the efficacy of metformin with respect to prevention of T2DM development in children should be studied in a longitudinal multi center randomized controlled trial, in which they are tracked into adulthood, before metformin is used in daily clinical practice in this population. However, since children with obesity are in general difficult to motivate to participate and to retain in longitudinal studies, it is questionable whether such a study will provide sufficient results [110]. For example, despite the fact that multiple strategies were used to motivate children to participate in the metformin trial, the intended inclusion number was not achieved. In addition, only 50% of the children included completed both the RCT and the extension study with a total follow-up of 36 months despite the use of motivational interviewing. Comparable dropout rates have been reported by others studies irrespectively of follow-up period. An even more important question is whether it is ethically justified to wait for evidence obtained from conventional longitudinal prospective studies (i.e. cohort studies and randomized controlled trials) in view of the current available literature, as this might unnecessary delay the optimization of the treatment of obesity and its related complications. Therefore, studies within the context of Learning Healthcare Systems where data collected during routine clinical care are used to manage and improve the processes, outcomes, and quality of healthcare, should be considered in this specific and complex population [111]. Since data are in this manner collected from and during daily clinical care visits, results directly reflect the actual clinical situation and patients can immediately benefit from treatment. We emphasize here that our studies on comorbidities such as asthma and ADHD (i.e. chapters 2 and 3) were also performed using data observed and registered during regular clinical treatment. The context of a Learning Healthcare System can also be of use to compare different diagnostic methods for example for cardiovascular disease, and for evaluation of therapies and diagnostic methods of comorbidities. In this respect it is of great importance to accurately record data in electronic patient files using

a standardized format so that data can be easily collected and evaluated. However, the question remains how the risk on missing data and lost to follow-up of patients can be minimized. In children this is of particular relevance as most children are referred back to the general practitioner when they become 18 years of age. A central system, such as a national electronic patient file using standardized formats might be a solution.

In conclusion, in this thesis we aimed to contribute to the treatment of comorbidity in children with obesity, screening for complications of obesity, and treatment of childhood obesity.

A high prevalence of potential overdiagnosis and as a consequence overtreatment of asthma was observed, as well as some undertreatment. Children with ADHD and obesity could be considered at risk for underdosing. This highlights the necessity for an accurate diagnostic process according to standardized protocols alongside with a dosing regimen based on the pharmacokinetic changes caused by obesity for each drug and regular evaluation of symptoms observed. This will lead to individualized treatment of common pediatric diseases in children with obesity.

Given the high prevalence of IR in both children and adolescents, and the increased arterial stiffness in adolescents with obesity compared to controls, screening on cardiometabolic complications should be performed in all children with obesity at yearly interval. Non-invasive screening methods for cardiometabolic complications in daily clinical care should be the focus of future research, since the best screenings method has not yet been elucidated. As children with obesity are in general difficult to motivate to participate and to retain in studies, the context of a Learning Healthcare System should be further explored in order to evaluate diagnostic and therapeutic approaches.

In the treatment of childhood obesity there seems to be a role for metformin, in addition to lifestyle intervention as drug for obesity and its related complications in both children and adults, given the favourable effect on BMI in children and adults, and the maintenance of weight loss and reduction in progression towards T2DM in adults. Metformin can be considered in (highly) motivated children with obesity and IR and/or impaired glucose intolerance. Since renal clearance in children with obesity is increased to adult levels the highest tolerated dosage, with a maximum of 3000mg/day as currently recommended in adults can be considered. The use of metformin should be evaluated annually based on achieved BMI and/or signs of complications such as IR, dyslipidemia, and hypertension. In addition, safety and tolerability should be part of the yearly assessment.

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