# Comorbidities, complications and treatment of childhood obesity

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# Section 4

## Treatment of childhood obesity

# Chapter 7

## Efficacy of metformin treatment with respect to weight reduction in children and adults with obesity, a systematic review

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## ABSTRACT

### Introduction

Obesity and its related complications are increasing health issues. Since generally only minor weight loss is obtained with lifestyle intervention, additional pharmacological therapies such as metformin are often used. We conducted a systematic review to provide an overview of the efficacy of ≥ 6 months metformin treatment in children and adults with respect to weight, insulin resistance, and progression towards type 2 diabetes mellitus (T2DM).

### Methods

In September 2018, we searched Pubmed, Embase, and The Cochrane library for studies published in English using the keywords metformin, obesity/overweight, and weight loss. Prospective studies reporting weight/body mass index (BMI) as primary or secondary outcome in patients with overweight/obesity with ≥ 6 months' metformin treatment were included. Included subjects were children and adults with overweight/obesity who received of ≥ 6 months of metformin and/or lifestyle intervention, and/or placebo and/or lifestyle intervention, and/or standard care. Studies were independently screened by two reviewers. Data were extracted by one and verified by the other reviewer, and both reviewers assessed the risk of bias using the Cochrane risk of bias tool.

### Results

Our review includes 15 pediatric and 14 adult studies. In children, after 6 months, more than half the studies reported a greater reduction in BMI with metformin versus controls. Only six studies had an intervention of > 6 months, and these studies found no further improvement in BMI in the metformin users, though their BMI was lower than that of controls. Three studies showed a significant improvement in insulin sensitivity in the metformin versus the control group. Adults using metformin experienced and maintained small decreases in weight irrespective of duration of intervention. In 11 of 14 studies, a greater reduction in weight/BMI was observed with metformin than incontrols. Progression toward T2DM was significantly reduced in adults using metformin, ranging from 7-31%. The safety and tolerability of metformin, withdrawals of participants, and comparison with other drugs were not taken into account.

### Conclusions

The effects of metformin on weight/BMI vary, with smaller reductions in children than in adults. This could be because of differences in adherence, daily dosage, and insulin status. Metformin significantly reduced the progression toward T2DM in adults. Therefore, metformin should be considered as a treatment for obesity and its related complications.

## INTRODUCTION

Obesity is an increasing health issue worldwide in both children and adults, with a prevalence in 2016 of 7.8% in boys, 5.4% in girls, 10.8% in man, and 14.9% in woman [1-3]. The prevalence is not only rising but also shifting toward a younger age, and the frequency of morbid obesity is increasing [4,5]. Consequently, complications associated with obesity, such as type 2 diabetes mellitus (T2DM), metabolic syndrome, cardiovascular disease, liver diseases, respiratory illnesses, and psychosocial problems, are now more frequent and are revealed at a younger age [3,4]. These complications mean that obesity is a substantial burden for patients and society, considering the health care cost and loss of productivity [6]. Although prevention of obesity is the ultimate goal, for now optimizing the treatment of obesity is crucial, particularly since it is known that about 80% of the children with obesity become adults with obesity [7,8].

Multidisciplinary lifestyle intervention is the cornerstone of the obesity treatment [9]. In clinical trials, a reasonable amount of weight loss is achieved with high-intensive lifestyle interventions in the majority of participants [10,11]. However, low-intensity lifestyle interventions, generally used in daily clinical practice, have been associated with only minor weight loss [9,10,12]. In addition, long-term maintenance of weight loss is difficult since relapse into old lifestyle habits and consequently weight gain is common [10]. Therefore, the search for additional (pharmacological) therapies alongside lifestyle intervention and psychological approaches to achieve and maintain meaningful weight loss is ongoing [10,13], particular since it has been shown that as little as 3% sustained weight loss improves cardiovascular risk factors, even though weight loss ≥ 5% is considered meaningful [10,14,15].

In adults, five drugs are currently registered as weight loss medications: orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion, and liraglutide [10,13,16]. Only orlistat has been registered for use as weight-loss medication in children aged ≥12years, and other drugs are being studied, including topiramate, exenatide, liraglutide, and metformin [10,13,16,17]. Of these drugs, metformin has been most studied.

Metformin is a biguanide that is associated with weight loss, probably due to a combination of its inhibition of gluconeogenesis, increased use of peripheral glucose, increased fatty oxidation in skeletal muscles, and inhibition of lipid synthesis in the liver, though the pharmacokinetics are not completely understood [18]. It is mainly excreted in the urine [18]. Metformin is currently registered for the treatment of T2DM in adults and in children ≥10 years of age [19]. However, it is now increasingly being used off label in both adults and children [20], as many studies have shown promising results regarding weight reduction in the short term (<6months) [19]. In addition, metformin has been associated with improvement of insulin sensitivity, and in adults it has been shown that metformin could play a role in delaying or even preventing the development

of T2DM [21-27]. Studies on the long-term (≥6months) efficacy of metformin are limited in both children and adults, especially studies with a duration of > 6 months. Moreover, an overview with respect to the effect of metformin on weight, insulin resistance, and progression to T2DM is lacking.

Therefore, the aim of this systematic review is to provide an overview of the effects of metformin regarding weight, insulin resistance, and progression towards T2DM in both children and adults with obesity of ≥ 6months.

## METHODS

### Eligibility criteria

Studies eligible for this review had to evaluate the long-term efficacy of metformin treatment on weight in patients with obesity. To be included, articles had to report on prospective studies with metformin treatment of at least 6 months with body weight/body mass index (BMI) as primary or secondary outcome parameter. Exclusion criteria were language other than English, animal studies, review articles, and clinical trials that evaluated metformin treatment in patients with diabetes, polycystic ovarian syndrome, drug induced obesity, and non-alcoholic fatty liver disease. We also excluded clinical trials without unique study data or with multiple drug interventions without a metformin-only subgroup or no control group without medications.

### Literature search and study selection

Literature searches were conducted in Pubmed, Embase, and The Cochrane library in September 2018 using he following keywords: metformin, weight loss, obesity, and overweight. The search strategy per database is displayed in the Supplementary Table 1. We also manually searched reference lists of included studies to find relevant articles not included in the original search.

All studies were imported into Refworks (www.refworks.com) and duplicates removed. Two reviewers independently screened titles and abstracts and subsequently the full-texts using the inclusion and exclusion criteria as described. Disagreements were resolved through discussion.

### Data extraction and management

The first reviewer extracted the following descriptive data from articles that fulfilled the inclusion criteria: study design and duration, eligibility criteria, intervention/control intervention, sample size, patients characteristics (age and BMI), outcomes regarding change in weight/BMI and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (in pediatric studies), and the incidence of T2DM in adults. The second re-

viewer verified these extracted data. If studies presented data at multiple timepoints, all timepoints were included in the analysis.

### Risk of bias assessment

The methodological quality of the included studies was independently assessed by both reviewers according to the Cochrane risk of bias tool. Elements of the risk of bias assessment included method of randomization and allocation concealment, masking of intervention, and data/outcome assessment.

### Analysis

Results were analyzed qualitatively and presented narrative form and in tables. No additional statistical analysis was performed. Outcomes regarding change in weight/BMI and HOMA-IR (in pediatric studies) were presented as mean +/- standard deviation score (SD), or median with range; and the incidence of T2DM (including reduction) is presented as a percentage.

## RESULTS

### Study selection

A total of 7179 articles (5932 unique studies) were identified using the search strategy presented in supplementary Table 1. Duplicates (n=1247), were removed and screening of titles and abstracts led to the exclusion of 5785 studies. The full text of the 147 remaining articles (57 pediatric and 90 adult studies) were critically appraised for eligibility, and 15 pediatric and 14 adult studies were included (Figure 1).

### Risk of bias/quality assessment

Of the 15 included pediatric studies, 14 were randomized controlled trails (RCTs) [28-41], and one was an open-label extension study [42]. According to the risk-of-bias-tool, 11 of the 14 RCTs were good quality and the remaining three were fair quality [29,34,36]. The open-label extension study was fair quality [42].

Of the 14 included adult studies, nine were RCT's [21,24,26,27,43-47], and five were open-label (extension) studies [22,23,25,48,49]. Of the nine RCT's, four were good quality [24,27,44,45], four were fair quality [21,26,43,46], and one was poor quality [47]. Of the five open-label (extension) studies, four were fair quality [22,23,25,49], and one was poor quality [48].

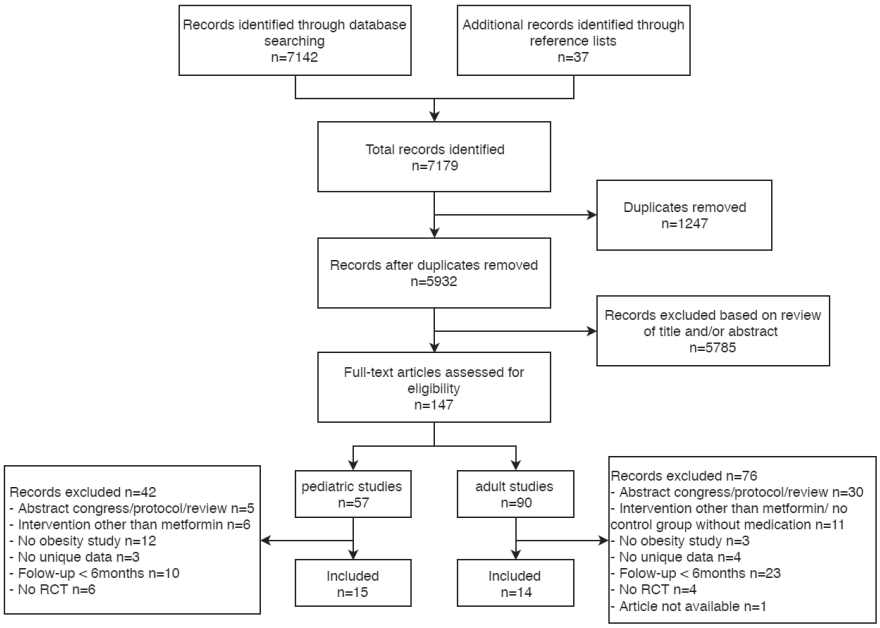


**Figure 1.** Flowchart of the search strategy
T1DM = type 1 diabetes mellitus; PCOS = polycystic ovary syndrome; RCT = randomized controlled trial

## Pediatric studies

*Study characteristics*

Table 1 provides an overview of the included pediatric studies, of which 14 of15 were RCT's and 1 of 15 was an open-label extension study. The number of participants per study ranged between 22 to 151 participants, with ages ranging from7 to19 years, and a BMI at study start between 27.4 to 40.1kg/m$^2$. Studies differed in number of study-arms (2-4), additional treatment, treatment of controls, and duration of intervention. In 9 of the 15 studies, all participants received metformin/placebo together with a comprehensive lifestyle intervention, including (structured) diet advice, physical activity, and motivational support or behavioral therapy [28,29,34-36,38-41]. The following comparisons were recorded: metformin versus placebo; metformin + comprehensive lifestyle intervention versus placebo + comprehensive lifestyle intervention; metformin versus standard care; and metformin + comprehensive lifestyle intervention with either vigorous or moderate exercise versus placebo + comprehensive lifestyle intervention with either vigorous or moderate exercise (Table 1). The duration of intervention ranged between 6 and 36 months. Three of six studies with an intervention period > 6 months also reported weight at interim timepoints, which are were included in the analysis**.**

**Table 1.** Overview of randomized controlled trials in children/adolescents, evaluating the effect of Metformin on BMI as a primary or secondary outcome

| Study | Study design and inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| *Studies with an intervention period of 6 months* | | | | |
| Atabek et al. 2008 [29] | 6 mo DB RCT<br>Age 9-17 years<br>Obesity (BMI ≥p95) | All lifestyle intervention<br>MET 1000mg vs. PLA | 90 MET, 30 CO<br>Mean age 11.8 (±2.8) years<br>Mean BMI 28.5 (±3.4) kg/m$^2$ | $\Delta BMI_{met}$-2.08kg/m$^2$ (±2.32) vs. $\Delta BMI_{co}$ +0.65kg/m$^2$ (±2.50); p<0.01<br>$\Delta HOMA\text{-}IR_{met}$ -3.74 (±3.8) vs. $\Delta HOMA\text{-}IR_{co}$ -1.05 (±2.3), ρ<0.01 |
| Clarson et al. 2009 [30] | 6 mo RCT<br>Age 10-16 years<br>Obesity (BMI ≥p95)<br>HOMA-IR >3.0 | All lifestyle intervention<br>With MET 1500mg vs. without MET | 11 MET, 14 CO<br>Mean age 13.1 ( 10.1-16.1) years<br>Mean BMI 35.2 (±1.5) kg/m$^2$ | $\Delta BMI_{met}$ -1.8 (0.8)kg/m$^2$ vs. $\Delta BMI_{co}$ +0.5 (0.3) kg/m$^2$; p<0.05<br>$\Delta HOMA\text{-}IR_{met}$ -0.5 (1.09) vs. $\Delta HOMA\text{-}IR_{co}$ -2.53 (1.02); p>0.05 |
| Freemark et al. 2001 [31] | 6 mo DB RCT<br>Age 12-19 years<br>BMI >30 kg/m$^2$<br>Insulin >15µU/ml<br>First or second degree family with T2DM | MET 1000mg vs. PLA | 14 MET, 15 CO<br>Mean age 14.9 (±0.6) years<br>Mean BMI 40.1kg/m$^2$ (±1.1) kg/m$^2$ | $\Delta BMI_{met}$ -0.5kg/m$^2$ vs. $\Delta BMI_{cos}$ +0.9kg/m$^2$ (p<0.02)<br>$HOMA\text{-}IR_{met}$ 119.5 ±14.1 to 64.0 ±5.2 vs.<br>$HOMA\text{-}IR_{con}$ 96.3 ±11.7 to 94.9 ±30.6 (p<0.01) |
| Kendall et al 2013 [32] | 6 mo DB, RTC<br>Age 8-18 years<br>BMI>98th centile on UK charts<br>IGT or hyperinsulinemia | MET 1500mg vs. PLA | 74 MET, 77 CO<br>Mean age 13.7 (±2.3) years,<br>Mean BMI: 36.5 (±6.3) kg/m$^2$ | $BMI_{met}$ 37.10 (±6.35)kg/m$^2$ vs. 36.85 (±6.29)kg/m$^2$<br>$BMI_{co}$ 35.95 (±6.32)kg/m$^2$ vs. 36.16 (±6.49)kg/m$^2$. Between groups p<0.01<br>$HOMA\text{-}IR_{met}$ 6.10 (3.00) vs. 6.30 (3.38)<br>$HOMA\text{-}IR_{co}$ 5.45 (2.99) vs. 5.74 (3.52) p>0.05. Between groups p=0.53 |
| Love-Osborne et al. 2008 [36] | 6 mo DB, RCT<br>Age 12-19 years<br>HOMA-IR >3.5 or FPI >25µU/ml<br>2 out of 3 risk factors: Acantosis nigricans, Obesity (>95 percentile) or family history T2DM | All lifestyle intervention<br>MET 1700mg vs. PLA | 48 MET, 16 CO<br>Mean age 15.7 years<br>Mean BMI 39.7 (range 28–55) kg/m$^2$ | $\Delta BMI_{met}$ −0.16 ± 1.89 kg/m$^2$ vs. $\Delta BMI_{con}$ +0.63 ± 1.29 kg/m$^2$; p=0.11 |

**Table 1.** Overview of randomized controlled trials in children/adolescents, evaluating the effect of Metformin on BMI as a primary or secondary outcome continued

| Study | Study design and inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| Mauras et al 2012 [37] | 6 mo RCT<br><br>Age 7-18 years, Uncomplicated obesity: BMI>95th percentile, normal BP, glucose tolerance, and total cholesterol | All lifestyle interventions<br><br>With MET 1000mg (<12 years of age) or 2000mg (≥12 years of age)<br>Vs. without MET | 23 MET, 19 CO<br>Mean age 12.2 (±0.5) years<br>Mean BMI 33.1 (±0.8) kg/m$^2$ | $\Delta BMI_{met}$ -2.4±0.5kg/m$^2$; p<0.01 vs. $\Delta BMI_{co}$ -1.1±0.5kg/m$^2$; p=0.04. Between groups: p=0.09<br><br>$\Delta HOMA\text{-}IR_{met}$ +0.34±0.76 (p=0.66) vs. $\Delta HOMA\text{-}IR_{co}$ +1.6±0.8 (p=0.06). Between groups no significant difference |
| Pastor-Villaescusa et al. 2017 [38] | 6 mo DB, RCT<br><br>7-14 years<br>BMI > 95th percentile | MET 1000mg vs. PLA | 68 MET, 72 CO<br>Age range 6.8-15.3 years<br>Mean BMI 29.1 (±0.7) kg/m$^2$ | *Prepubertal subgroup*<br>$\Delta BMI_{met}$-1.7 (±0.7) kg/m$^2$ vs. $\Delta BMI_{co}$ -1.0 (±0.6)kg/m$^2$; p=0.19<br><br>$\Delta HOMA\text{-}IR_{met}$ -0.1 (±0.2) vs. $\Delta HOMA\text{-}IR_{co}$ 0.1 (±0.3); p=0.72<br><br>*Pubertal subgroup*<br>$\Delta BMI_{met}$ -0.4 (±0.5)kg/m$^2$ vs. $\Delta BMI_{co}$ -0.9 (±0.4)kg/m$^2$; p=0.22<br><br>$\Delta HOMA\text{-}IR_{met}$ +0.2 (±0.4) vs. $\Delta HOMA\text{-}IR_{co}$ 0.0 (±0.4); p=0.73 |
| Schrinivasan et al. 2006 [33] | 2x 6 mo DB crossover RCT<br><br>Age 9-18 years<br>Obesity<br>FPI/FPG >4.5 or presence of acanthosis nigricans | MET 2000mg and PLA | 10 MET/CO, 12 CO/MET<br>Mean age 12.5 (±2.2) years<br>Mean BMI 35.2 (±5.1) kg/m$^2$ | Metformin had a greater treatment effect over placebo for weight -4.35kg, p=0.02,<br>BMI -1.26 kg/m$^2$, p<0.01, |
| Wiegand et al 2010 [39] | 6 mo DB RCT<br><br>No success of 6 lifestyle intervention (ΔBMI <2.0)<br>Age 10-17 years, BMI >97th percentile, HOMA-IR >3.0 or >95th percentile | All lifestyle intervention<br><br>MET 1000mg vs. PLA | 36 MET, 34 CO<br>Mean age 15.1 years<br>Mean BMI 34.9 (±5.4) kg/m$^2$ | $\Delta BMI_{met}$ +0.07 vs. $\Delta BMI_{co}$ +0.31 (p=0.96)<br><br>$\Delta HOMA\text{-}IR_{met}$: -0.55 vs. $\Delta HOMA\text{-}IR_{co}$ -1.05; p=0.86 |

**Table 1.** Overview of randomized controlled trials in children/adolescents, evaluating the effect of Metformin on BMI as a primary or secondary outcome continued

| Study | Study design and inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| *Studies with an intervention of ≥ 12 months* | | | | |
| Warnakalasuriya et al. 2018 [40] | 12-mo Triple blinded RCT<br><br>Age 8-16 years<br>BMI ≥2SD for age | All diet and psychical activity training<br><br>MET 1000mg (<11 years) or 2000mg (≥11 years)<br>vs. PLA | 68 MET, 82 CO<br>Mean age 12.1 (±2.3) years<br>Mean BMI 27.4 (2.8) kg/m$^2$ | 6 months:<br>$\Delta BMI_{met}$ -0.9 (-1.2 to -0.6) kg/m$^2$ vs. $\Delta BMI_{co}$ -0.05 (-0.3 to +0.2) kg/m$^2$ (p<0.01)<br>$\Delta HOMA\text{-}IR_{met}$ -0.06 (-0.07 to +0.7) vs. $\Delta HOMA\text{-}IR_{co}$ 0.3 (-0.4 to + 1.0) (p=0.45)<br><br>12months:<br>$\Delta BMI_{met}$ -0.9 (-1.2 to -0.5) kg/m$^2$ vs. $\Delta BMI_{co}$ -0.06 (-0.4 to +0.8) kg/m$^2$ (p<0.01)<br>$\Delta HOMA\text{-}IR_{met}$ -1.8 (-2.6 to -1.0) vs. $\Delta HOMA\text{-}IR_{co}$ -0.8 (-1.5 to -0.04) (p=0.08) |
| Vd Aa et al. 2017 [42] | 18 mo DB RCT<br><br>Age 10-16 years<br>BMI-sds>2.3<br>HOMA-IR ≥3.4<br>Caucasian descent | All lifestyle intervention<br><br>MET 2000mg<br>vs. PLA | 23 MET, 19 CO<br>Median age 12.8 (11.3 to 15.3) years<br>Median BMI 30.2 (28.1 to 38.6) kg/m$^2$ | $\Delta BMI_{met}$ +0.2 (−2.9 to 1.3) kg/m$^2$ vs. $\Delta BMI_{co}$ +1.2 (−0.3 to 2.4) kg/m$^2$ (p=0.02)<br><br>$\Delta HOMA\text{-}IR_{met}$ -1.0 (-3.2 to 2.3) vs. $\Delta HOMA\text{-}IR_{co}$ -0.16 (-1.7 to 1.5) p=0.28 |
| Clarson et al. 2014 [35] | 24 mo DB RCT<br>Age 10-16 years<br>Obesity (BMI >p95) | MET ER 2000mg + moderate exercise vs. MET extended release 2000mg + vigorous exercise vs. PLA + moderate exercise vs. PLA + vigorous exercise<br><br>NB: Moderate or vigorous exercise program during 12 weeks, thereafter weekly exercise with all participants together | 6 mo analysis<br>16 MET moderate, 15 MET vigorous; 14 CO moderate, 16 CO vigorous)<br>Mean age 13.7 (±2.1) years<br>Mean BMI 32.5 (±5.6) kg/m$^2$<br><br>FU 24 mo: 6 MET moderate, 4 MET vigorous; 9 CO moderate, 10 CO vigorous) | 6 months:<br>$BMI_{metMod}$ 31.56 (5.19) vs. 31.11 (5.44)kg/m$^2$ p<0.01<br>$BMI_{metVig}$ 34.43 (5.67) vs. 32.20 (6.80) kg/m$^2$; p<0.01<br>$BMI_{CoMod}$ 31.96 (5.09) vs. 32.35 (5.62) kg/m$^2$; p NS<br>$BMI_{CoVig}$ 32.15 (6.34) vs. 32.26 (5.64) kg/m$^2$; p NS<br><br>$HOMA\text{-}IR_{metMod}$ 3.2 (±2.8) to 1.9 (±1.2); p<0.01)<br>$HOMA\text{-}IR_{metVig}$ 3.3(±1.5) to 2.5 (±1.6); p=NS<br>$HOMA\text{-}IR_{CoMod}$ 3.3(±1.4) to 4.0 (±2.5) P=NS<br>$HOMA\text{-}IR_{ConVig}$ 4.3 to 2.6; p<0.01.<br><br>12 months:<br>Improvements were maintained, but not incrementally improved.<br><br>24months:<br>No further improvements in BMI and HOMA-IR. Although interpretation was limited due to a small number of participants |

**Table 1.** Overview of randomized controlled trials in children/adolescents, evaluating the effect of Metformin on BMI as a primary or secondary outcome continued

| Study | Study design and inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| Wilson et al. 2010 [41] | 100 wk DB RCT<br>4 weeks run-in phase, 48 weeks intervention and 48 weeks follow-up<br><br>Age 13-18 years<br>BMI ≥95th percentile | All lifestyle intervention<br><br>MET ER 2000mg vs. PLA | 27 MET, 19 CO<br>Mean ag 14.9 (±14.4) years<br>Mean BMI 35.9 (±5.2) kg/m$^2$ | 52 weeks:<br>$\Delta BMI_{met}$ -0.9 (±0.5)kg/m$^2$<br>vs. $\Delta BMI_{cos}$ +0.2 (±0.5)kg/m$^2$; p=0.03<br>$\Delta HOMA\text{-}IR_{met}$ -0.1 (±0.8)<br>vs. $\Delta HOMA\text{-}IR_{cos}$ -0.8 (±0.7); p=0.48<br><br>52-100 weeks:<br>$\Delta BMI_{met}$ +0.5 (±0.5)kg/m$^2$<br>vs. $\Delta BMI_{co}$ -0.8 (±0.5)kg/m$^2$; p=0.02<br>$\Delta HOMA\text{-}IR_{met}$ -0.4 (±0.9)<br>vs. $\Delta HOMA\text{-}IR_{co}$ +0.5 (±0.8); p=0.44 |
| Yanovski et al. 2011 [34] | 6 mo DB, RCT followed by 6 mo open-label treatment for all participants<br><br>Age 6-12 years<br>BMI ≥95th percentile<br>FPI ≥15µU/mL | MET 2000mg vs. PLA | 45 MET, 40 CO<br>Mean age 10.3 (±1.5) years<br>Mean BMI 34.4 (±6.5) kg/m$^2$ | 6months:<br>$\Delta BMI_{met}$ -0.78 (-1.54 to -0.01 kg/m$^2$<br>vs. $\Delta BMI_{co}$ +0.32 (-0.54 to +1.18)kg/m$^2$ p<0.01<br>$\Delta HOMA\text{-}IR_{met}$ +0.68 (-0.4 to +1.76)<br>vs. $\Delta HOMA\text{-}IR_{co}$ +2.23 (+1.02 to +3.43) p<0.01<br><br>12months:<br>Significant decrease in BMI in subjects new on metformin<br>Non-significant increase in BMI in subjects continuously on metformin. |
| Lentferink et al. 2018 [43] | 18 mo open-label extension study following an 18 mo DB, RCT [42] | MET 2000mg for participants with BMI-sds>2.3,HOMA-IR ≥3.4 and consent for MET treatment vs. no treatment | 5 MM, 14 MP, 6 P**M, 6 PP***<br>Media age 14.7 (11.6 to 17.9) years<br>Median BMI 30.7 (22.3 to 45.1)kg/m$^2$ | 18-36months<br>$\Delta BMI_{MM}$ 2.2 (0.2 to 9.0) kg/m$^2$<br>vs. $\Delta BMI_{MP}$ 1.9 (-1.8 to +8.5) kg/m$^2$<br>vs. $\Delta BMI_{PM}$ 0.5 (-2.1 to +5.1) kg/m$^2$<br>vs. $\Delta BMI_{PP}$ 1.1 (0.5 to +3.1)kg/m$^2$ (p=0.89)<br><br>$\Delta HOMA\text{-}IR_{MM}$ 13.7 (1.6 to 48.3)<br>vs. $\Delta HOMA\text{-}IR_{MP}$ 11.2 (-5.4 to +29.4)<br>vs. $\Delta HOMA\text{-}IR_{PM}$ 1.1 (-4.6 to +1.4)<br>vs. $\Delta HOMA\text{-}IR_{PP}$ 0.4 (-0.8 to =2.2) (p=0.14) |

Mo = months, DB= double blind, RCT = randomized controlled trial, BMI= body mass index, PLA = placebo MET = metformin, CO = control, HOMA-IR = The homeostatic model assessment for insulin resistance, T2DM = type 2 diabetes mellitus, UK =United Kingdom, IGT= impaired glucose tolerance, FPI=fasting plasma glucose, BP = blood pressure, FPG = fasting plasma glucose, sds= standard deviation score, ER=extended release, FU = follow-up, NS = non-significant, MM = Metformin during RCT and Metformin during open label extension study, MP – Metformin during RCT and Placebo (= no medication) during open label extension study, PM = Placebo during RCT and Metformin during open label extension study, PP = Placebo during the RCT and Placebo (=no treatment) during the open label extension study.

*BMI*

Of the 15 included pediatric studies, 12 reported BMI at 6 months [28-39]. In all of these studies, a stabilization (n=1) or a decrease (n=11) in BMI was observed, in the metformin group, with a range of -2.4 to +0.02kg/m$^2$. In six of the 12 studies, the control group showed an increase in BMI, ranging between +0.11 to +0.9 kg/m$^2$, and in the remaining six studies a decrease ranging from -0.05 to -1.1 kg/m$^2$. Compared with placebo, a significant reduction in BMI in the metformin group was observed in eight studies [28-34,39]. The remaining four studies observed no differences between the groups [35-37].

Six of the included studies had an intervention period > 6 months: 12, 18, 24, and 36 months [33,34,39-42]. Warnakulsuriya et al 2018, Yanovski et al 2011, and Clarson et al 2014, reported results at different timepoints and did not observe further reductions in BMI beyond 6 months of treatment [33,34,39]. Wilson et al., van der Aa et al., and Lentferink et al 2018, reported only the final outcomes [40-42]. Wilson et al. showed a significant reduction in BMI in the metformin versus the placebo group at 12 months [40]. Van der Aa et al. found a significant smaller increase in BMI in the metformin versus the placebo group at 18 months [41]. In the open-label study of Lentferink et al., an initial decrease in BMI was observed in metformin naïve patients, whereas patients continuing on experienced an increase in BMI [42]. In all four studies, the maximum effect of metformin was observed during the first 6-9 months of treatment [34,40-42].

*HOMA-IR*

With respect to HOMA-IR, three studies showed a significant reduction in the metformin versus placebo group [28,30,34]. One study showed a significant smaller increase in HOMA-IR in the metformin versus the placebo group [33]. The remaining studies did not observe significant differences between the groups for HOMA-IR [29,31,32,35-42].

*Daily dosage*

The prescribed metformin dosage per day differed between the studies namely from 1000 to 2000mg per day. In two of the four studies prescribing metformin 1000mg per day observed a significant difference in BMI change between the metformin and the placebo group [35,38], whereas this was the case for 9 of11 studies prescribing metformin 1500-2000mg per day [29,31-34,36,39-41].

## Adult studies

*Study characteristics*

Table 2 provides an overview of the included adult studies, of which 9 of 14 were RCTs, and 5 of 14 were open-label (extension) studies. The number of participants per study ranged between 32 and 3234 participants, with a mean age ranging from 39.1 to 55.2

years, and a mean BMI at study start ranging from 25.8 to 35.9kg/m$^2$. Studies differed in the number of study-arms (2 to 4), additional treatment, treatment of controls, and duration of intervention. The following comparisons were recorded: metformin versus placebo; metformin versus standard care; metformin + (comprehensive) lifestyle intervention versus placebo + (comprehensive) lifestyle intervention; metformin versus placebo versus (comprehensive) lifestyle intervention; (comprehensive) lifestyle intervention versus metformin + (comprehensive) lifestyle intervention versus standard care; (comprehensive) lifestyle intervention versus metformin versus standard care; metformin versus. metformin + (comprehensive) lifestyle intervention versus (comprehensive) lifestyle intervention versus standard care (Table 2). The duration of intervention ranged between 6 months and 15 years.

*Weight/BMI*

Of the 14 included adult studies, four reported weight change at 6 months [43,44,48,49]. Three of these studies found that weight and/or BMI decreased significantly more in the metformin tan in the placebo or untreated control groups [44,48,49], whereas another study did not observe differences between the groups [43]. Alibasic et al. also included a lifestyle group; however no significant difference in weight reduction was observed compared with the metformin group [48].

Four other studies reported weight changes at 12 months [25,27,45,46]. In two of these studies BMI/weight decreased significantly more in the metformin than in the placebo group [27,45], whereas the other two studies did not observe differences between the groups [25,46].

Six studies had an intervention period of ≥ 18 months [21-24,26,47]. Of these studies Iqbal Hydrie et al. observed significant more weight loss in the metformin group than in a standard care group after 18 months, but the metformin group did not lose more weight than the lifestyle group [26]. At 24 months, Schuster et al. observed a significant decrease in weight/BMI in the metformin group, whereas the placebo group showed a significant increase [47]. Ramchandran et al. observed a stabilization in weight in the metformin group at 30 months, but the untreated control group increased in weight [24]. This study also included a lifestyle group and a combination of lifestyle + metformin group [24]. The lifestyle group increased in weight at 24 months, and the combination group did not show significant differences in weight during the study period [24]. The diabetes prevention program research group studies included lifestyle, metformin, and placebo groups [21-23]. The average weight loss after an median of 2.8 years of intervention (range 1.8 to 4.6 years), was 0.1kg in the placebo, 2.1kg in the metformin, and 5.6kg in the lifestyle group ($p<0.01$) [21,23]. After an median intervention period of 10 years (range 9.0 to 10.5 years), the weight loss achieved in the original placebo and metformin group was maintained; however, in the lifestyle group, weight gradually

**Table 2.** Overview of randomized controlled trials in adults, evaluating the effect of Metformin on BMI as a primary or secondary outcome

| Study | Study design And inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| *Studies with an intervention period of 6 months* | | | | |
| Alibasic et al. 2013 [49] | 6 mo prospective study<br><br>abnormal glycoregulation and prediabetes | LSI<br>vs. LSI + MET1000mg,<br>vs. CO (SC) | LSI 20, MET 20, CO 20<br>Age 45-80 years<br>BMI 32.8 kg/m$^2$ (only reported for MET) | Weight$_{lsi}$-4.25kg, BMI$_{lsi}$-1.3kg/m$^2$ (both p<0.05)<br>Weight$_{met}$ -3.83kg, BMI$_{met}$-1.33kg/m$^2$ (both p<0.05)<br>Controls no significant reduction in weight or BMI (numbers not reported) |
| Lethovirta et al. 2001 [44] | 6 mo RCT, followed by 6 months FU without treatment<br><br>Age 35-70 years<br>BMI 25-35 kg/m$^2$<br>First degree relative with T2DM<br>IGT >12months | MET 1000mg<br>vs. PLA | MET 20, CO 20<br>Age range 35-70 years,<br>BMI range 25-35 kg/m$^2$ | 6 mo:<br>Weight$_{met}$ 91.0kg ±17.9 to 88.4kg ±18.8<br>vs. Weight$_{co}$ 87.8kg ±18.8 to 86.6kg ±17.9; p=0.07 |
| Seifarth et al. 2013 [50] | Outpatient clinic setting,<br>6 mo treatment<br><br>BMI ≥27kg/m$^2$<br>Insulin resistance | MET doses based on BMI (BMI <30kg/m$^2$: 1500mg, BMI ≥30 to <35 kg/m$^2$ : 2000mg, BMI ≥35kg/m$^2$ 2500mg) vs. no treatment | 154 MET, 45 CO<br>Mean age 39.1 (±12.2) years<br>Mean BMI 35.2 (±5.3) kg/m$^2$ | Weight$_{met}$ -5.8 ± 7.0kg (5.6 ± 6.5%)<br>vs. Weight$_{co}$ +0.8 ± 3.5kg (+0.8 ± 3.7%); p<0.01 |
| Worsley et al. 2015 [45] | 36 wk DB, RCT<br><br>Female sex<br>Aged 35 – 65<br>BMI ≥30 - <40kg/m$^2$ and/or waist circumference ≥88 cm | MET 1700mg<br>vs. PLA | 44 MET, 49 CO<br>Mean age 53.2 (±7.3) years<br>Mean BMI 32.9 (±5.0)kg/m$^2$ | BMI$_{met}$ -1.0 kg/m$^2$ ; 95% CI -1.37 to -0.62<br>vs. BMI$_{co}$ -0.1; 95% CI -0.29 to 0.28; p<0.01) |
| *Studies with an intervention period of 12 mo* | | | | |
| Andreadis et al. 2008 [25] | 12 mo interventional multifactorial open label<br><br>≥18 years (40-79 years)<br>BMI > 27kg/m$^2$ | All lifestyle advice and drug management for CVD risk factors<br><br>With MET 850mg vs.without MET | 95 MET, 271 CO<br>Mean age 53.0 ±0.5 years<br>Mean BMI 32.3 ±0.2kg/m$^2$ | BMI$_{met}$ -0.9 (±0.5)<br>vs. BMI$_{co}$ -0.6 (±0.1); p=0.11.<br><br>Incidence of T2DM: $_{met}$ 1.1 vs. $_{co}$ 8.1%, (risk difference = −7% 95% CI −12.7% to −1.4%, p=0.01). |

**Table 2.** Overview of randomized controlled trials in adults, evaluating the effect of Metformin on BMI as a primary or secondary outcome continued

| Study | Study design And inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| Fontbonne et al. 1996 [46] | 12 mo DB, RCT<br><br>Age 35-60 years (men); 40-65 years (woman) high waist-to-hip ratio (men: ≥0.95; women: ≥0.80). | All lifestyle advice<br><br>MET 1700mg vs. PLA | MET 164, CO 160<br>Mean age 49.5 ±6.6years<br>Median BMI 33.1 (24.2-45.3) kg/m$^2$ | Weight$_{met}$ -2.0 (-3.0 to -1.1) vs. Weight$_{co}$ -0.8 (-1.6 to +0.1); p<0.06 |
| Li et al. 1999 [27] | 12 mo DB, RCT<br><br>Age 30-60 years<br>IGT | MET 750mg vs. PLA | 33 MET, 37 CO<br>Mean age 49.5 ±1.2 years<br>Mean BMI 26.2 ±2.3kg/m$^2$ | BMI$_{met}$ 26.4 ±2.3kg/m$^2$ to 25.0 ±2.2kg/m$^2$<br>vs. BMI$_{co}$ 26.0 ±2.3kg/m$^2$ to 26.4 ±2.4kg/m$^2$; p<0.01 between groups<br><br>T2DM incidence MET 3.0% vs. PLA 16.2% p=0.01 |
| Obrien et al. 2017 [47] | 12 mo RCT<br><br>Latino ethnicity<br>Female sex<br>≥20 years<br>IGT | LSI vs. MET 1700mg vs. SC | NLSI 30, MET 27, CO 28<br>Mean age 45.1 (±12.5)years<br>Mean BMI 33.3 (±6.4)kg/m$^2$ | Weight$_{met}$ -0.9kg, 1.1% vs. Weight$_{lsi}$ -4.0kg, 5.0% vs. Weight$_{co}$ +0.8, 0.9%; p<0.01<br>BMI$_{met}$ -0.4kg/m$^2$ vs. BMI$_{lsi}$ -1.6kg/m$^2$ vs. BMI$_{co}$ +0.3kg/m$^2$; p<0.01<br><br>LSI significant larger weight and BMI changes than MET and CO (both p<0.01).<br>MET not significant larger weight and BMI changes than CO (p=0.28). |
| *Studies with an intervention period ≥ 18 months* | | | | |
| Knowler et al. 2002 [21] DPP | DB RCT, average FU 2.8 years<br><br>Age ≥25 years<br>BMI≥24kg/m$^2$<br>FPG (5.3-6.9 mmol/l) and 2 hours glucose 7.8- 11.0 mmol/l | MET 1700mg vs. LSI vs. PLA | MET 1073, LSI 1079, CO 1082<br>Mean age 50.6 (±10.7) years<br>Mean BMI 34.0 (±6.7) kg/m$^2$ | Weight$_{met}$ -2.1kg vs. Weight$_{lsi}$ -5.6kg vs. Weight$_{co}$-0.1kg.<br>LSI lost significantly more weight than placebo and MET (p<0.01).<br><br>MET reduced T2DM incidence by 31% (95% CI, 17-43%), LSI by 58% (95% CI 48-66%), as compared with PLA |

**Table 2.** Overview of randomized controlled trials in adults, evaluating the effect of Metformin on BMI as a primary or secondary outcome continued

| Study | Study design And inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| Diabetes prevention program research group 2009 [22] DPPOS | Open label extension study after completion of DB RCT [21] Average FU 10.0 (9.0-10.5) years<br><br>Surviving DPP No withdrawn consent irrespective of whether they had developed diabetes | All group-implemented LSI<br><br>With MET 1700mg vs. without MET. | 924 MET, 910 LSI, 932 CO Mean age 55.2 (±10.4) years Mean BMI 35.9 (±5.9)kg/m$^2$ | $Weight_{met}$ -1.7kg since DPP randomization. Maintained weight loss throughout DPPOS (-2.1 to -1.7kg). $Weight_{lsi}$ -2.3kg since DPP randomization. Gradually regained weight throughout DPPOS (-5.6 to -2.3kg) $Weight_{co}$ -1.0kg since DPP randomization. Some weight loss throughout DPPOS (-0.1 to -1.0kg).<br><br>T2DM incidence reduced by 18% (95% CI 7–28) in MET group and in LSI group 34% (24–42) compared with PLA. |
| Diabetes prevention program research group 2015 [23] DPPOS | Open label extension study after completion of DPP: DB RCT [21], average FU 15 years<br><br>Surviving DPP; No withdrawn consent irrespective of whether they had developed diabetes | All group-implemented LSI<br><br>With MET 1700mg vs. without MET | 924 MET, 910 LSI, 932 CO Mean age 55.2 (±10.4) years Mean BMI 35.9 (±5.9) kg/m$^2$ | $Weight_{metn}$ -3.5kg since DPP randomization $Weight_{lsi}$ -3.5kg since DPP randomization $Weight_{co}$ -2.3kg since DPP randomization<br><br>T2DM incidence reduced by 18% (p<0.01) in MET group vs by 27% (p<0.01) in LSI group compared with PLA. |
| Iqbal Hydrie et al. 2012 [26] | 18 mo RCT<br><br>Age >30 years IGT | SC vs. LSI vs. LSI + MET 1000mg | CO 82, LS 107, MET 85 Mean age 43.6±9.8years Mean BMI 27.1 ±4.9 kg/m$^2$ | $Weight_{met}$ -1.37kg vs. $Weight_{lsi}$ -0.12kg vs. $Weight_{co}$ +0.96kg;<br><br>MET lost significant more weight than CO p<0.01. No difference between MET and LSI.<br><br>T2DM risk reduction of 11.5% in MET group and 10.7% in LSI group compared with CO |

**Table 2.** Overview of randomized controlled trials in adults, evaluating the effect of Metformin on BMI as a primary or secondary outcome continued

| Study | Study design And inclusion criteria | Intervention | Participants | Outcome |
|---|---|---|---|---|
| Ramachandran et al. 2006 [24] | RCT mean FU 30 months<br><br>IGT on two occasions<br>35-55 years | MET 500mg<br>vs. LSI + MET 500mg<br>vs. LSI<br>vs. CO | MET 128,<br>MET+LSI 121, LSI 120, CO 133<br>Mean age<br>45.9±5.7 years<br>Mean BMI<br>25.8±3.5 kg/m$^2$ | $Weight_{met}$ no significant differences.<br>$Weight_{metLsi}$ no significant differences.<br>$Weight_{lsi}$ significant increase at T=24 (p=0.04).<br>$Weight_{con}$ significant increase at all timepoints (p<0.01).<br>The relative risk reduction of T2DM was 26.4% with MET (95% CI 19.1–35.1, p=0.03),<br>28.2% with LSI + MET (95% CI 20.3–37.0, p=0.02),<br>28.5% with LSI (95% CI 20.5–37.3, p=0.02) as compared with CO |
| Schuster et al. 2004 [47] | 24 mo DB, RCT<br>First degree relatives of African Americans with T2DM<br>Normal glucose tolerance<br>Obesity | MET 500mg<br>vs. PLA | 45 MET, 81 CO<br><br>Mean age and BMI not reported | $Weight_{met}$ -1.4 ± 1.0kg; p<0.02<br>$Weight_{co}$ +1.4±0.8kg; p<0.02<br><br>$BMI_{met}$ -0.53 ± 0.4kg/m$^2$; p<0.01<br>$BMI_{co}$ +0.50±0.34 kg/m$^2$; p<0.01 |

Mo = months, LSI, = lifestyle intervention, MET = metformin, CO = control, SC = standard care, FU = follow-up, BMI= body mass index, RCT = randomized controlled trial, PLA = placebo, T2DM = type 2 diabetes mellitus, IGT= impaired glucose tolerance, DB= double blind, FPG = fasting plasma glucose, DPP = diabetes prevention program, DPPOS = diabetes prevention program outcome study. *Knowler et al 2002, diabetes prevention program research group.

increased although their weight was still approximately 2kg less than at randomization [22,23]. After 15 years of intervention, weight regain in the lifestyle group and sustained weight loss in the metformin group led to almost identical weight loss in the metformin and lifestyle group [23]. Weight slightly decreased in the placebo group after 8 to 9 years of follow-up, but the weight loss achieved was still less than that in the metformin and lifestyle group [23]. The maximum achieved weight loss was observed after 1 year of intervention in the lifestyle group (-6.9kg) and after 15 years in the metformin and placebo groups (-3.5kg and -2.3kg respectively) [23].

*Progression towards T2DM*

Seven studies reported on the incidence of T2DM, with all reporting that the incidence of T2DM was lower in the metformin group, with a risk reduction between 7 and 31% compared with placebo or standard care [21-26]. Participants in these studies were diagnosed with overweight/(morbid) obesity and IGT, except those in the study by Andreadis et al.) and treated with metformin for durations ranging from 12 months to

15 years. In the study by Iqbal Hydrie et al. and of Ramachandran et al. the risk reduction of T2DM in the metformin group was comparable with that in the lifestyle intervention group after an intervention period of 18 and 30 months, respectively [24,26]. In the diabetes prevention program research group studies, the initial risk reduction after a median follow-up of 2.8 years was higher in the lifestyle intervention than in the metformin group: 58% versus 31% compared with placebo [21]. The difference in risk reduction between the lifestyle and the metformin groups declined as the duration of the intervention increased; after 15 years of follow-up, the risk reduction was 27% for lifestyle intervention and 18% for metformin compared to placebo, respectively [21-23].

*Daily dosage*

Major differences in daily metformin dosages prescribed were observed between the studies, ranging between 500 and 2500mg. Four of seven studies with a daily metformin dosage ≤ 1000mg showed a significant decrease in weight/BMI compared with controls [26,27,47,48]. In two of the four studies reporting a significant difference, participants had overweight instead of obesity at baseline (BMI 26.2 -27.1kg/m$^2$) [26,27], and one did not report the BMI [47]. In four of seven studies with a daily dosages of metformin of ≥ 1700mg, a significant decrease in weight/BMI was observed compared with controls [44-46,49]. In the three studies prescribing ≥ 1700mg metformin but not reporting a significant decrease in weight/BMI compared with controls, the mean BMI at study start was the highest of all included studies: 34.0-35.9kg/$^2$) [21-23].



## DISCUSSION

The aim of this review was to evaluate the efficacy of ≥ 6 months of metformin treatment in children and adults with obesity with respect to weight, insulin resistance, and progression toward T2DM. To date, few studies have evaluated the long-term efficacy of metformin treatment in children and adults with obesity. Most studies performed in both children and adults had an intervention period of ≤ 6 months [28-32,35-38,43,44,48,49]. In the current review. only six pediatric, and ten adult studies were found with an intervention period > 6 months [21-27,33,34,39-42,45-47]. In the pediatric studies, the maximum effect of metformin was generally observed in the first 6-9 months of treatment, after which some regain of weight was observed. Since the BMI at the end of intervention/study period was generally lower in the metformin than in the control groups, there might be an indication for metformin treatment [33,34,39-41]. This is in contrast to findings in adults, where the achieved weight loss was maintained even after 15 years of intervention [21-23,26,27,45,47].

Some factors may have contributed to this difference. First, it should be mentioned that BMI levels and consequently the cut-of values of a normal/healthy BMI, in children rise physiologically with age [50]. Therefore, stabilization of BMI in growing children can be considered a beneficial effect, and change in BMI may consequently underestimate the actual obtained effect of any weight loss intervention over time in children [50,51]. Minor BMI changes in children with metformin treatment might therefore reflect a higher improvement in weight than weight changes observed in adults. Weight loss of > 5%, which is considered meaningful in adults, can therefore not be used as an indicator of successful weight loss in children [14,52]. More reliable observations regarding BMI change can be made using the age- and sex-specific BMI-z or BMI-sds scores [51]. However, since only a few studies reported BMI-z/BMI-sds we have presented only absolute BMI.

The daily metformin dosage might also have influenced the observed effect of metformin on weight in both pediatric and adult studies. The maximum advised daily metformin dosage is currently 2000mg a day in children and 3000mg in adults [53]. Interestingly, the prescribed daily dosage was often higher in the pediatric studies, ranging from 1000 to 2000mg, whereas in the adults studies, the daily doses ranged between 500 and 2500mg [24,47,49]. Hence, it might be concluded that many participants in both pediatric and adult studies received an inadequate daily dosage of metformin and consequently were undertreated, which might have limited the effect regarding weight/BMI reduction. However, while the percentage of pediatric studies observing a difference in weight was higher among those receiving a higher dosage, no clear association was observed between the prescribed daily dosage and the effect on weight/BMI in adults. However, it should be mentioned that a difference in baseline BMI might have influenced this observation in adults [21-23,26,27,35,38]. This observation is in line with results reported by McDonagh et al.; their review of pediatric studies found a small difference in effect (more BMI reduction with higher daily metformin dosages) [54]. Results of a recent pediatric study also suggest that the effect of metformin could be dosage dependent, as a significant decrease in BMI-z was only observed in prepubertal children who received a higher dosage per kilogram of weight compared with pubertal children (19.6mg/kg ±0.74 vs. 13.4 ±0.38mg/kg) [37].

A recent pharmacokinetic study showed that the clearance of metformin in subjects with obesity is higher than in lean counterparts, in both children and adults [55]. The clearance of adolescents with obesity was comparable to that in adults without obesity, suggesting that the maximum daily doses of metformin could be safely raised up to the maximum advised adult dosage of 3000mg a day [55]. Hence, the question could be raised whether the currently maximum advised daily doses of 3000mg a day in adults could also be safely raised [55], especially in hose with morbid obesity.

Another factor that might explain differences in effect regarding weight/BMI change between studies and between pediatric and adult populations is the adherence to therapy. In both pediatric and adult studies, this is suggested to be a major component determining the efficacy of metformin treatment [35,56]. Love Osborne et al. observed that subjects adherent to metformin regimens decreased BMI to the greatest extend, though subject with low adherence to metformin still gained less weight than adherent subjects receiving placebo [35]. In that study, weight loss was also correlated linearly with metformin adherence, as subjects with excellent adherence to metformin were most likely to decrease BMI by 5% [35]. On the other hand, subjects non-adherent to placebo gained the most weight [35]. In the diabetes prevention program study, adherence was also strongly associated with weight loss in the metformin subgroup and the duration of weight loss [22,56]. A total of 48% of subjects with high adherence and only 27% of those with low adherence to metformin treatment reported a ≥ 5% weight reduction [56]. It should also be noted that 27% of participants high adherent to placebo lost ≥ 5% weight, which suggests that low adherence to metformin is equivalent to no additional therapy [56]. This is in contrast with the observation by Love-Osborne et al., who found that subject low adherence to metformin lost weight, whereas participants with low adherence to placebo did not, suggesting that the metformin itself, not solely therapy adherence, is a relevant factor for weight loss [35].

The fact that participant in the pediatric studies started to regain weight shortly after initial weight loss might be related to a decrease in adherence, possibly related to puberty, which is known to be a turbulent stage. In addition, puberty is associated with a physiological increase in insulin resistance, which might have influenced the effect of metformin with respect to changes in HOMA-IR [57,58]. It has also been suggested that metformin would have a larger impact on weight in subjects with more severe insulin resistance [49]. Differences in weight loss between included studies and between pediatric and adult studies could therefore be partly related to insulin resistance status. Furthermore, eligibility criteria included insulin resistance in most pediatric studies, but IGT in most adult studies, suggesting more severe insulin resistance.

Incidence of T2DM is often the primary outcome in metformin studies in adults, which was true for seven of the 14 adult studies in the current review. In all seven studies, a reduction in incidence of T2DM was observed in subjects using metformin compared with controls (i.e., placebo or standard care), with reductions ranging from 7% to 31% [21-27]. It should be mentioned that the reduction in incidence of T2DM in patients receiving a lifestyle intervention was higher than in those receiving metformin, with reductions ranging from 27% to 58% compared with controls [21-24]. However, as long-term adherence to lifestyle intervention in daily clinical practice is known to be difficult to maintain, results of metformin seem promising [10]. Metformin is not yet registered as a treatment for obesity, since the average weight loss of ≥ 5% considered meaningful has not been

observed in trials in adults [21-27]. However, improvements in cardiovascular risk factors have been observed after weight loss as small as 3% [10,14,15]. This raises the question as to whether meaningful weight loss of ≥ 5% should be used as criteria to qualify a drug for registration as an obesity treatment, since the purpose of treatment is eventual reduction of complications and not weight reduction itself. A reduction of T2DM incidence was reported in adults using metformin, but an average weight loss ≥5% was not obtained [21-27]. Therefore, metformin should be considered as a useful drug in the treatment of obesity and related complications and registered for this purpose. In particular, since a 10-year cost-benefit analysis showed that lifestyle intervention is cost effective but metformin was cost saving [59], metformin could achieve a major reduction in healthcare costs by preventing/delaying T2DM and its complications [6].

To whom metformin should be prescribed remains unclear. Since severity of insulin resistance seems to be a determinant of metformin efficacy, it seems reasonable to prescribe metformin only to subjects with obesity and insulin resistance and/or prediabetes. Adherence to therapy also seems to be a major determinant of the efficacy of metformin, since the percentage of meaningful weight loss in patients highly adherent to metformin was almost twice as high as in patients with low adherence [56]. Since adherence to therapy depends on patients motivation and thereby the efficacy of metformin treatment, it seems rational to consider metformin only in (highly) motivated patients. As the clearance of metformin is known to be increased in subjects with obesity, dosages should be adjusted accordingly. This becomes even more important since morbid obesity is becoming increasingly more frequently observed. The current maximum daily dosage is 2000mg in children and 3000mg in adults, which are considered safe and therefore increments of the current dosages should be considered [55].

Ideally, longitudinal intervention studies starting in childhood should be conducted to evaluate the efficacy of metformin. Since studies on obesity are generally limited by low inclusion numbers and high levels of withrawal, studies should be performed within a formation of research networks to accomplish adequate inclusion numbers [60]. In addition, studies in daily clinical practice usin a standardized protocol may be considered as more practical counterpart to RCTs.

### Limitations

Only studies published in the English language were evaluated, which means we may have excluded potentially eligible studies. In addition, safety and tolerability of metformin was not evaluated and compared with other interventions; therefore this could not be taken into account in considering whether or not to recommend metformin treatment. This also applies for withdrawals of participants.

## CONCLUSION

The effects of metformin on weight/BMI vary, with smaller reductions in children than in adults. This could be caused by differences in adherence, daily dosage, and insulin status. Metformin significantly reduced the incidence of T2DM in adults. Therefore, metformin should be considered as treatment for obesity and its related complications.

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## COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: Y. Lentferink, C. Knibbe, and M. van der Vorst declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: For this type of study formal consent is not required.

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## SUPPLEMENTARY MATERIAL TO CHAPTER 7

**Supplementary Table 1.** Search strategies of literature search.

| Database | Search strategy |
|---|---|
| Pubmed | Search (((((“obesity”[MeSH Terms] OR “obesity”[All Fields])) OR (“overweight”[MeSH Terms] OR “overweight”[All Fields])) AND (“metformin”[MeSH Terms] OR “metformin”[All Fields]))) AND (“weights and measures”[MeSH Terms] OR (“weights”[All Fields] AND “measures”[All Fields]) OR “weights and measures”[All Fields] OR “weight”[All Fields] OR “body weight”[MeSH Terms] OR (“body”[All Fields] AND “weight”[All Fields]) OR “body weight”[All Fields]) Filters: English |
| Embase | (‘obesity’/exp OR obesity) AND (‘metformin’/exp OR metformin) AND (‘weight, mass and size’ OR ‘body weight’ OR ‘weight reduction’) AND [english]/lim |
| The Cochrane library | ((obesity.ti,ab or overweight.ti,ab) AND (metformin.ti,ab) AND (weight.ti,ab or weight loss. ti,ab or body mass index.ti,ab)) |