

Obesity Prevention

Treatment of clinical insulin resistance in children: a systematic review

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Summary

The objective of this study was to evaluate the effectiveness of interventions aimed at improving clinical insulin resistance and/or pre-diabetes in children. This study is a systematic review and meta-analysis. Five electronic databases were searched for randomized controlled trials of at least 2-months' duration. The outcomes were fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), body mass index (BMI) and adverse outcomes. Four randomized controlled trials were identified. All compared the effect of 6 months of metformin plus or minus lifestyle intervention with placebo plus or minus lifestyle intervention. After pooling results from three trials, the mean difference after 6 months favoured the intervention with a statistically significant mean decrease in fasting insulin, HOMA-IR and BMI of $9.6 \mu\text{U mL}^{-1}$ (95% confidence interval [CI]: 6.3, 13.0 $\mu\text{U mL}^{-1}$; $I^2 = 76\%$), 2.7 (95% CI: 1.7, 3.6; $I^2 = 74\%$) and 1.7 kg m^{-2} (95% CI: 1.1, 2.3 kg m^{-2} ; $I^2 = 75\%$) respectively. Mild gastrointestinal symptoms were reported in 19% (2–29%; median and range) of participants taking metformin. Metformin improves markers of insulin sensitivity and reduces BMI in children and adolescents with clinical insulin resistance or pre-diabetes. Stronger evidence from high-quality studies of longer duration and larger sample size are required before clinical conclusions about the optimal treatment protocol in this population can be drawn.

Keywords: Children, insulin resistance, pre-diabetes, systematic review.

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Introduction

While the incidence of type 2 diabetes remains low in the general paediatric population, certain countries, including the USA (1) and Australia (2), have identified gradually increasing rates. Between 1999 and 2004 in the USA, and 2001 and 2006 in Australia, the proportion of type 2 diabetes among new-onset diabetes in children and adolescents increased to 45% (1) and 11% (3) respectively.

Despite the low detection rate of type 2 diabetes in obese children and adolescents who are screened, there is a high prevalence of insulin resistance and pre-diabetes (4). Both insulin resistance and pre-diabetes have been shown to be reversible through pharmacological and lifestyle interven-

tions (5). Therefore, early identification and effective treatment may help slow the increasing prevalence of type 2 diabetes in children and adolescents (6).

A relationship exists between body mass index (BMI), insulin resistance and pre-diabetes, but it is not a consistent one, and therefore, cannot be viewed as a simple continuum. Guidelines currently exist for treatment of pre-diabetes in adults (7,8). However, despite the large body of literature on insulin resistance in children and adolescents, there are currently no guidelines for its treatment. It has been suggested that paediatric cases of insulin resistance and pre-diabetes can be managed with metformin if an individualized lifestyle treatment plan has been unsuccessful (9). However, there are also concerns about prescribing

medications to children without adequate evidence from clinical studies supporting their safety and efficacy (10).

The purpose of this systematic review is to examine the effectiveness of treatments that have been trialled for children and adolescents with clinical insulin resistance or pre-diabetes.

Methods

Inclusion and exclusion criteria

The review included all randomized controlled trials (RCTs) of at least 2-month duration that studied the effectiveness of treatments for insulin resistance and/or pre-diabetes in participants who were ≤ 19 years of age.

Insulin resistance was defined as the presence of overweight or obesity (International Obesity Task Force cut-points (11), BMI $> 30 \text{ kg m}^{-2}$, or > 85 th percentile for age and sex), with one or more of acanthosis nigricans, elevated fasting insulin, fasting insulin to glucose ratio, homeostasis model assessment of insulin resistance (HOMA-IR) or altered measure of insulin resistance or sensitivity as indicated by an oral glucose tolerance test (OGTT), modified minimal model frequently sampled intravenous glucose tolerance test (SI_{MM}) or euglycaemic clamp. Because of inter-assay and inter-laboratory influences on the interpretation of insulin levels, no cut-points for the above measures were defined prior to the search.

Pre-diabetes was defined using the American Diabetes Association classification: impaired fasting glucose (fasting blood glucose between 5.6 and 6.9 mmol L⁻¹), or impaired glucose tolerance (2 h post-load between 7.8 and 11.0 mmol L⁻¹) (12).

Studies were excluded if recruitment of participants was exclusively based on weight, BMI and/or skin-folds; participants had type 1 or type 2 diabetes; insulin resistance or pre-diabetes was syndromal or was secondary to treatment, such as chemotherapy.

Outcomes

The primary outcomes were BMI (kg m^{-2}) and indices of insulin sensitivity, i.e. fasting insulin ($\mu\text{U mL}^{-1}$) or homeostasis model assessment insulin resistance ($\text{HOMA-IR} = \text{fasting insulin } [\mu\text{U mL}^{-1}] \times \text{fasting glucose } [\text{mmol L}^{-1}] / 22.5$). BMI z-score was not included because of there being insufficient data from included trials. The secondary outcomes assessed were adverse events experienced.

Search strategy for identification of studies

Electronic searches

On 22 October 2008, a systematic databases search was performed on Ovid MEDLINE (1950–22 October 2008), CINAHL (1982–October 2008), Cochrane Central

Register of Controlled Trials, EMBASE and PsychINFO (1967–October week 2 2008).

Initially, seven keyword categorical searches were carried out on Ovid MEDLINE (Appendix 1) (i) Insulin resistance, or metabolic syndrome, or polycystic ovarian syndrome, or acanthosis nigricans, or insulin, or hyperinsulin(a)emia, or glucose tolerance test; (ii) Pre-diabetic state or glucose intolerance; (iii) Child, or adolescent, or p(a)ediatrics; (iv) Lifestyle; (v) Metformin; (vi) Exercise, or exercise therapy, or resistance training, or physical education/training, or physical activity and (vii) Diet, or diet therapy, or child nutrition physiology, or adolescent nutrition physiology, or dietary carbohydrates, or dietary fat. Categories 1–2 were combined, then added to category 3 to obtain all trials in paediatric populations with insulin resistance or pre-diabetes. These results were then added to each of categories 4–7 to obtain all trials in this population applying one or more of these four interventions. The search was then limited to RCTs published in English. Searches of the other four databases were carried out on the same day using a modified version of the above search strategy.

Study selection

The search strategy (Appendix 1) yielded 211 trials from Ovid MEDLINE while the modified versions yielded 27 trials from CINAHL (1982–2008), 55 from Cochrane Central Register of Controlled Trials, 180 from EMBASE and 3 from PsychINFO. The titles of these 476 trials were reviewed using the defined criteria and duplicates were removed leaving 41 trials, Fig. 1. The abstracts of these 41 RCTs were reviewed and 36 papers excluded because recruitment was exclusively based on weight and/or BMI, or the RCT objective was treatment of obesity, diabetes, polycystic ovarian syndrome or precocious puberty. The authors of five RCTs were contacted, two in order to clarify whether hyperinsulinaemia was part of the inclusion criteria. After correspondence with one of these two authors, the trial (13) was excluded. As of October 2008, four trials were eligible for inclusion in our systematic review.

Study assessment

Data relating to the methodological, clinical and statistical components of each trial were extracted by one reviewer (SQ) and checked by two reviewers (LB and SG). The JAMA criteria (14) were used to critically appraise the study methodology in order to determine the validity of the RCT results. The primary criteria assessed whether assignment of patients to treatments was randomized and whether all patients were accounted for and attributed at the trial conclusion. The secondary criteria assessed whether patients, health workers and study personnel were 'blind' to treatment allocation, whether groups were

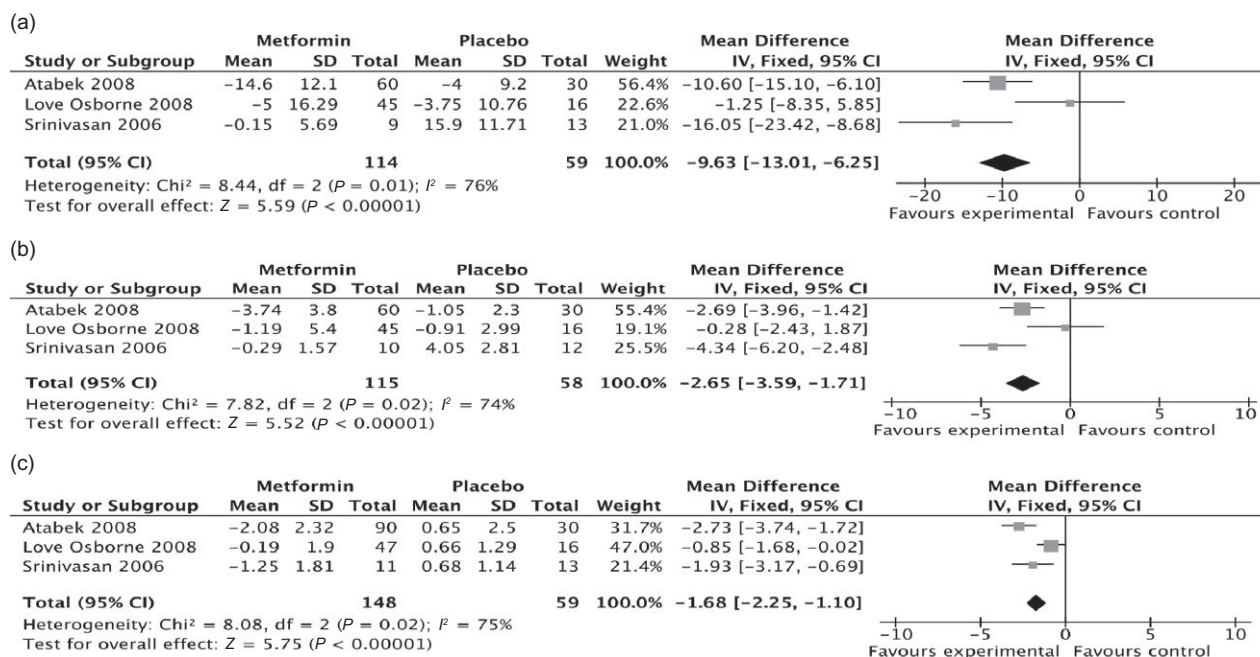


Figure 1 (a) Pooled results for the effect of 6 months of metformin on plasma fasting insulin ($\mu\text{U mL}^{-1}$) compared with placebo. Comparison: metformin \pm lifestyle intervention vs. placebo \pm lifestyle intervention; Outcome: change in plasma fasting insulin ($\mu\text{U mL}^{-1}$) at 6 months. (b) Pooled results for the effect of 6 months of metformin on homeostasis model assessment of insulin resistance (HOMA-IR) compared with placebo. Comparison: metformin \pm lifestyle intervention vs. placebo \pm lifestyle intervention; Outcome: change in HOMA-IR at 6 months. (c) Pooled results for the effect of 6 months of metformin on body mass index (BMI) (kg m^{-2}) compared with placebo. Comparison: metformin \pm lifestyle intervention vs. placebo \pm lifestyle intervention; Outcome: change in BMI (kg m^{-2}) at 6 months.

similar at the start of the trial and whether the groups were treated equally except for the experimental intervention.

Data synthesis

Three of the five contacted authors made additional clinical and statistical data available. Two authors provided raw data (15,16) and in this circumstance, the means and standard deviations for baseline and 6-month data were determined, and the mean difference and standard deviations were calculated by subtracting baseline data from 6-month data to determine the size of the treatment effects. For each of these studies, there was one extreme outlier in the intervention group at 6 months, each with a fasting insulin >3 standard deviations from the mean.

The data provided by one author (17) included the 64 participants ($n = 48$ in the intervention group and $n = 16$ in the control group) that completed the trial. No baseline and follow-up data were available for the 90 participants that were initially randomized and therefore the results could only be calculated from the data of the 64 participants that completed the trial.

The other study for which raw data were made available was a randomized crossover trial (16). As the authors had noted a period effect, the decision was made to only analyse the data from the first 6-month phase of this trial. While

this reduced the number of participants in the intervention and control group it made the study comparable with the other three trials with respect to duration and baseline characteristics.

After systematically reviewing the studies, pooling of the results was performed using Review Manager 5 (Review Manager [RevMan] Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Results from one trial (15) could not be included in the pooled analysis because standard deviations were not known. A pooled weighted mean difference for the continuous data was obtained and associated 95% confidence intervals (CIs) were generated. To quantify the effects of heterogeneity the chi-squared and I^2 -squared test were performed by Review Manager 5. A further subgroup analysis was performed to compare the results of combined metformin lifestyle trials (17,18) with the sole placebo-controlled metformin trial (16) that was suitable for review in the meta-analysis.

Results

Literature search results

Four RCTs were identified (15–18), three of which had sufficient data for inclusion in a meta-analysis (16–18). All

trials compared various doses of metformin with placebo, while the two most recent (17,18) added lifestyle intervention to both the treatment and control group. No studies comparing lifestyle interventions alone were identified.

Quality of included trials

Using the criteria (14) defined above, the methodology of the four trials was critically appraised (Table 1). Three trials (15–17) provided sufficient information on the methodologies used to validate the results of the trials. Two trials (16,17) stated the method of allocation concealment, one of which used computer generated random allocation (16) while in the other, the research centre pharmacist randomly allocated participants (17). These two studies however had 6-month follow-up data on less than 80% of participants; only one trial (16) clearly stated the reason for each participant's discontinuation and therefore had no loss to follow-up. All trials were double-blinded although none stated whether outcome assessors were blinded to treatment allocation. Aside from the experimental intervention, both treatment and control groups were treated equally in all trials.

Study description

Table 2 outlines the different study populations, inclusion criteria, interventions and duration used in each of the four trials. The crossover trial (16) was twice as long as the other three trials; however, because of the previously noted period effect, only data from the first 6-month phase of the trial were used. All studies were conducted in children aged 9–18 years. One trial stratified participants into early (<2) and late (≥ 3) Tanner stages (16), two trials included specific Tanner stages (2–4 (18) and 3–5 (15)), while pubertal stage was unspecified in the remaining trial (17). The study population in two studies (16,17) was predominantly made up of ethnic groups known to have a high prevalence of clinical insulin resistance. All adolescents were obese and had insulin resistance with one or more of a fasting insulin $>15 \mu\text{U mL}^{-1}$ (15,17), fasting insulin (mU) to glucose (mmol L $^{-1}$) ratio >4.5 (16) or HOMA-IR >3.5 (17). One study (18) stated that the participants had hyperinsulinaemia but did not define this in the inclusion criteria.

Two trials (15,18) started with a maximum metformin dose of 500 mg b.i.d. and continued this for 6 months, while the other trials (16,17) gradually increased the metformin dose to 1000 mg b.i.d. over 3 weeks, or to 850 mg b.i.d. over 2 months respectively. Two trials (17,18) also included individually tailored exercise and dietary lifestyle interventions in both the treatment and control groups (Table 2).

Impact of treatment on markers on fasting insulin and homeostasis model assessment of insulin resistance

The pooled mean difference after 6 months of metformin, with or without lifestyle intervention, showed a statistically significant decrease in fasting insulin of $9.6 \mu\text{U mL}^{-1}$ (95% CI: 6.3, 13.0 $\mu\text{U mL}^{-1}$; $I^2 = 76\%$) and a decrease in HOMA-IR of 2.7 (95% CI: 1.7, 3.6; $I^2 = 74\%$) (Fig. 1a,b). If the two extreme outliers in two of the studies (16,17) were included in the analysis, the results remained significant. The decrease in fasting insulin was $7.7 \mu\text{U mL}^{-1}$ (95% CI: 3.9, 11.5 $\mu\text{U mL}^{-1}$; $I^2 = 66\%$) and decrease in HOMA-IR was 2.1 (95% CI: 1.1, 3.1; $I^2 = 58\%$) (data not shown). The placebo-controlled metformin trial (16) had a greater overall mean decrease in fasting insulin of $16.1 \mu\text{U mL}^{-1}$ (95% CI: 8.7, 23.4 $\mu\text{U mL}^{-1}$) and HOMA-IR 4.3 (95% CI: 2.5, 6.2) compared with combined metformin lifestyle interventions (17,18), which had a pooled mean decrease of $7.9 \mu\text{U mL}^{-1}$ (95% CI: 4.1, 11.7 $\mu\text{U mL}^{-1}$; $I^2 = 79\%$) and 2.1 (95% CI: 1.0, 3.2; $I^2 = 72\%$) respectively (data not shown).

In the placebo-controlled metformin trial (16), with the outlier excluded, the fasting insulin in the metformin group decreased by $0.2 \pm 5.7 \mu\text{U mL}^{-1}$ after 6 months and the placebo group increased fasting insulin by $15.9 \pm 11.7 \mu\text{U mL}^{-1}$ (Fig. 1a). Hence, the difference between groups was $16.1 \mu\text{U mL}^{-1}$ (95% CI: 8.7, 23.4 $\mu\text{U mL}^{-1}$). With respect to the two trials that combined metformin with lifestyle interventions (17,18), the lifestyle intervention in the placebo group resulted in a decrease in fasting insulin from baseline of $3.8 \pm 10.8 \mu\text{U mL}^{-1}$ (17) and $4.0 \pm 9.2 \mu\text{U mL}^{-1}$ (18); although a greater decrease in fasting insulin was seen in the combined metformin lifestyle intervention, the overall mean decrease was not as large as that seen in the placebo-controlled metformin trial. A similar trend was seen for the HOMA-IR results.

Impact of treatment on body mass index

Figure 1b shows a statistically significant pooled mean decrease in BMI of 1.7 kg m^{-2} (95% CI: 1.1, 2.3 kg m^{-2} ; $I^2 = 75\%$) between the metformin with and without lifestyle intervention when compared with placebo with and without lifestyle intervention after 6 months of intervention. Including the two extreme outliers had a negligible effect on the overall pooled mean difference, with a resultant decrease of 1.7 kg m^{-2} (95% CI: 1.1, 2.0 kg m^{-2} ; $I^2 = 79\%$) (data not shown). With the outlier included in the placebo-controlled metformin trial (16), the overall mean decrease in BMI of 2.8 kg m^{-2} (95% CI: 0.8, 4.8 kg m^{-2}) was greater than the combined metformin lifestyle interventions (17,18), which had a pooled mean decrease of 1.6 kg m^{-2} (95% CI: 0.9, 2.2 kg m^{-2} ; $I^2 = 88\%$) (data not

Table 1 Validity of trial results appraised using the JAMA criteria (14)

	Freemark and Bursley, 2001 (15)	Srinivasan <i>et al.</i> , 2006 (16)	Love-Osborne <i>et al.</i> , 2008 (17)	Atabek and Pirgon, 2008 (18)
Primary guides				
Was the assignment of patients to treatments randomized?	Yes Stratified by sex and ethnicity	Yes Block randomization, stratified by pubertal stage	Yes Stratified by ethnicity and fasting insulin (<40 µU mL ⁻¹ or >40 µU mL ⁻¹)	Yes No stratification
Method of allocation concealment	Method not stated	Computer-generated random number allocation	Research centre pharmacist	Method not stated
Were all patients properly accounted for and attributed at trial completion?				
Was follow-up complete	91% (T = 93% C = 88%)	79% (T = 77% C = 80%)	75% (T = 80% C = 64%)	Not clear
Intention to treat analysis	Not clear	Not clear	Not clear	Not clear
Included in final analysis	29 (T = 14 C = 15) included one non-compliant participant and one who took a reduced dose	22 (T = 10 C = 12); non-compliant subjects were included	64 (T = 48 C = 16)	Not stated
Excluded from final analysis	3 (T = 1 C = 2) discontinued in first 6 weeks for reasons not related to drug toxicity	6 (T = 3 C = 3), 4 discontinued (1 in each group did not like taking tablets, 2 in group receiving placebo in phase 1 had other commitments), 2 in group receiving metformin in phase 1 could not be cannulated	21 (T = 12 C = 9) discontinued trial: 3 (T = 2 C = 1) because of side effects, 6 (T = 4 C = 3) after first visit (only 1 had lost weight)	Appears to be none. States that no patients dropped out because of side effects
Secondary guides				
Were patients, health workers and study personnel 'blind' to treatment?	Double-blinded; no indication of whom	Participants and investigators blinded. Unblinding occurred after final data analysis	Participants and investigators blinded	Participants and investigators blinded
Outcome assessor blinded to treatment allocations	Not stated	Not stated	Not stated	Not stated
Were groups similar at the start of the trial	Table 1 – BMI was significantly higher (7.2%) in the metformin group (mean BMI: T = 41.5 C = 38.7 kg m ⁻²)	Paper states there was no difference in baseline characteristics between group receiving placebo and group receiving metformin in phase 1	Table 1 – treatment and control groups were not matched precisely for ethnic background, gender or initial BMI	Paper states no significant difference between groups
Aside from experimental intervention were groups treated equally?	Yes	Yes	Yes	Yes

BMI, body mass index; C, control group; T, treatment group.

Table 2 Comparison between study population, interventions and adverse events experienced

Author (year, state, country)	Sample, <i>n</i> (randomized/analysed), <i>n</i> in each arm (M/F), Tanner (T) stage	Age (range, mean \pm SD)	Ethnicity	Inclusion criteria	Metformin: complete duration, dose loading regime, max dose duration	Lifestyle intervention		Adverse events: GIT Non-GIT
						Control	Intervention	
							Exercise	Diet
Freemark and Bursey, 2001 (15) NC, USA	<i>n</i> = 32/29 (3 dropouts not included) T: 14 (3/11) C: 15 (8/7) T stage ≥ 3	12–19 T: 14.4 ± 0.6 C: 15.4 ± 0.5	T: 64% White, 36% Black C: 45% White, 55% Black	BMI > 30 kg m ⁻² Ins ⁰ > 15 μ U mL ⁻¹ Family history of type 2 diabetes	6 months, no dose loading, 1000 mg d ⁻¹ (500 mg b.i.d.) for 6 months	Placebo	Not stated	No dietary restrictions GIT T: 4/14 (28.6%) of which 1/14 (7%) changed dose because of persistent nausea C: 1/15 (0.1%) Non-GIT T: 1/14 (7%) migraine C: 0/15
Srinivasan <i>et al.</i> , 2006 (16) NSW, Australia	<i>n</i> = 28/22 (data from phase 1*) T: 13 C: 15 Stratified to T stage (<2/ ≥ 3)	9–18 12.5 \pm 2.2	64% high prevalence (Pacific Island, India); 25% Northern European; 11% mixed	International Obesity Task Force definition of obesity plus either/or • FIGR > 4.5 • acanthosis	6 months, gradually increased dose over 3 weeks to 2000 mg d ⁻¹ (1000 mg b.i.d.) for 5 months and 1 week	Placebo	Standardized information on health eating was provided†	Standardized information on health eating was provided† GIT T: 2/13 (15.5%) both changed dose because of persistent nausea C: 0/15
Love-Osborne <i>et al.</i> , 2008 (17) CO, USA	<i>n</i> = 85/64 (90 is stated in the text?) T: 60 (17/43) C: 25 (8/17) T stage not taken into account	12–19 T: 15.5 ± 1.7 C: 14.2 ± 4.6	58% Hispanic; 34% African-American	Ins ⁰ > 25 μ U mL ⁻¹ and/or HOMA-IR > 3.5 plus 2 of • BMI > 95th percentile for age and sex • acanthosis • family history of type 2 diabetes	6 months; gradually increased dose over 2 months: first month – 500 mg d ⁻¹ , second month – 1000 mg d ⁻¹ (500 mg b.i.d.); 1700 mg d ⁻¹ (850 mg b.i.d.) for final 3 months	Placebo	Regular aerobic exercise recommended	2 of 3 individually determined goals: • positive changes • decreasing negative choices • smaller portions Recommended reduced calories, fats and simple sugars, and increased fruit, vegetables and fibre
Atabek and Pirgon, 2008 (18) Konya, Turkey	<i>n</i> = 120 T: 90 (45/45) C: 30 (15/15) T stage 2–4	9–17 T: 11.83 ± 2.8 C: 11.6 ± 2.7	Not stated	BMI > 95th percentile for age and sex; hyperinsulinaemia	6 months, no dose loading, 1000 mg d ⁻¹ (500 mg b.i.d.) for 6 months	Placebo	≥ 30 min d ⁻¹ of exercise recommended	Individually tailored recommendations targeting an energy intake of 30 kcal kg ⁻¹ of current body weight (50% CHO, 30% fats, 20% protein) GIT T: 2/90 (2.2%) C: 0/30

*To make this crossover study comparable with the other trials, in terms of baseline characteristics and duration, only data from phase 1 were used in the pooled analysis.

†Individualized intensive lifestyle changes were not part of the intervention therefore this trial was considered a placebo-controlled metformin trial.

n, number of participants; M, male; F, female; b.i.d., twice daily; BMI, body mass index; T, treatment; C, control; FIGR, fasting insulin to glucose ratio; HOMA-IR, homeostasis model assessment of insulin resistance; Ins⁰, fasting insulin; *n*, number of participants; GIT, gastrointestinal tract; CHO, carbohydrates.

shown). All placebo control groups, whether receiving lifestyle interventions or not, had a similar increase in BMI (Fig. 1c).

Trial heterogeneity

For each meta-analysis performed the chi-squared statistic had a *P*-value of <0.1 and a *I*-squared test of >50%, indicating heterogeneity between the trials results (Fig. 1). Despite this heterogeneity in trial results, the studies all had a similar age range of the participants, trial interventions and follow-up duration. Pooling of results was therefore carried out.

Adverse events reported

Nineteen per cent (2–29%; median and range) of participants in the metformin group reported mild transient gastrointestinal side effects, such as nausea, diarrhoea and abdominal discomfort. The highest percentage (29%) was reported in the earliest trial (15) where dose loading was not used to control early gastrointestinal side effects (Table 2). Two 9-year-old participants in one trial (16) and one participant in another trial (15) required a decrease in the metformin dose in order to control mild but persistent nausea. Only one trial (17) reported participant withdrawal because of the mild adverse event – two were receiving metformin and one was receiving placebo. No severe adverse events, such as vomiting or lactic acidosis, were experienced by any of the participants in any of the trials. One participant on metformin reported exacerbation of migraine.

Discussion

This systematic review identified four RCTs on treatment of clinical insulin resistance and/or pre-diabetes in children and adolescents, all of which looked at the effectiveness of metformin used alone or in combination with lifestyle interventions. Although no trials on lifestyle interventions alone were identified, this systematic review shows that metformin, whether used alone or in combination with lifestyle interventions, improves markers of insulin sensitivity, fasting insulin and HOMA and reduces BMI.

Several features of clinical insulin resistance, including hyperinsulinaemia, hyperlipidaemia and hypertension, are risk factors for type 2 diabetes or cardiovascular disease. With the increasing incidence of type 2 diabetes in adolescents, there has been a growing awareness for the need to treat clinical insulin resistance and pre-diabetes in this population. Consequently three RCTs were published in 2008 (17–19). Unfortunately, one (19) of these only became available 2 months after the database search for this systematic review was completed, and hence was not included in this review.

To date, all RCTs have focused on the use of metformin, alone or in combination with lifestyle interventions. No results from RCTs on lifestyle interventions alone were identified. The lifestyle interventions used in the two included RCTs were based on individually determined goals (17) or recommendations (18) rather than on structured classes or education sessions. The outcomes of the interventions are therefore dependant on the motivation and self-discipline of the participants. Future studies should include a more formalized and detailed approach to lifestyle intervention.

Results from the RCTs presented and other longitudinal studies have shown that weight status (20) and insulin resistance (21) are likely to continue to worsen over time unless intensive lifestyle or pharmacological interventions are pursued. In two trials (17,18), individualized lifestyle interventions plus placebo had a positive short-term effect on decreasing fasting insulin and HOMA-IR; however, BMI continued to increase at a similar rate to that in the trials where placebo group received no lifestyle intervention (15,16,19). The combined effect of metformin and individualized lifestyle intervention resulted in the greatest decrease in fasting insulin and had the additional effect of decreasing BMI.

There are several limitations to the review. First, the sample size of included trials was small and only three were suitable for inclusion in the meta-analysis, making subgroup analysis difficult to perform. Hence the statistical power, even after pooling of data, is low. Of the two studies driving the overall effect of the meta-analysis, one (18) provided insufficient detail on methodology to draw conclusions about the validity of the results, and the other (16) had a decrease in fasting insulin of only $0.2 \pm 5.7 \mu\text{U mL}^{-1}$ after 6 months of metformin despite the large mean difference seen between the treatment and control group.

Second, of the three trials that provided sufficient detail to determine attrition rate (15–17), the mean value was 20%, with more people in the control group (25%) compared with the intervention group (16%) discontinuing trial participation. This highlights the difficulties with implementing treatment regimens in this age group. One study (17) had a particularly high attrition rate in both the control (36%) and intervention arm (33%); the authors attributed this to the prolonged dose loading regimen of 2 months decreasing the impact of the intervention on weight loss and consequently resulting in participant dissatisfaction with the treatment.

Third, we need to consider the effects of inter-assay, inter-laboratory and intra-individual variation in measuring insulin sensitivity, on pooling fasting insulin and HOMA-IR results. An accurate and standardized immunoassay for measuring fasting insulin is currently not available. Of the included trials, only two (16,18) used the same type of immunoassay, and one trial (17) used two labora-

tories for measuring insulin. In addition, it has been recommended that the mean of three samples taken at 5-min intervals should be used to minimize intra-individual variation (22). This was not done in any of the included trials.

Finally, there is the issue of whether the markers of insulin sensitivity used, fasting insulin and HOMA-IR, provided the optimal method for outcome assessment. The euglycaemic clamp technique, often considered to be the gold standard method for measuring insulin sensitivity, was not used in any of the trials as it is too expensive and technically difficult to use for large scale research purposes. Two of the included trials (15,16) measured insulin sensitivity using the modified minimal model; however, this method did not result in a statistically significant increase in insulin sensitivity. It has been suggested that the minimal model may not be able to detect small changes in insulin sensitivity in severely obese patients (23). Hence, considering the population and short trial duration, fasting insulin and HOMA-IR were considered the most clinically and practically relevant option.

In summary, our systematic review and meta-analysis suggests that individually tailored lifestyle interventions, when combined with metformin, have a positive effect on reducing both fasting insulin and BMI in children and adolescents with clinical insulin resistance and/or pre-diabetes in the short to medium term. This systematic review is, however, unable to conclude what intervention is most effective as there are only a small number of pharmacological trials and no non-pharmacological trial currently available.

Conflict of interest statement

All authors declare that there is no conflict of interest.

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References

- Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr* 2005; **146**: 693–700.
- McMahon SK, Haynes A, Ratnam N. Increase in type 2 diabetes in children and adolescents in Western Australia. *Med J Aust* 2004; **180**: 459–461.
- Craig ME, Femia G, Broyda V, Lloyd M, Howard NJ. Type 2 diabetes in Indigenous and non-Indigenous children and adolescents in New South Wales. *Med J Aust* 2007; **186**: 497–499.
- Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents. National health and nutrition examination survey 2005–2006. *Diabetes Care* 2009; **32**: 342–347.
- Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, Khunti K. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* 2007; **334**: 299.
- Fonseca VA. Early identification and treatment of insulin resistance: impact on subsequent prediabetes and type 2 diabetes. *Clin Cornerstone* 2007; **8**: S7–S18.
- Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman R. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007; **30**: 753–759.
- Twigg SM, Kamp MC, Davis TM. Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association. *Med J Aust* 2007; **186**: 461–465.
- Caprio S. Treatment of impaired glucose tolerance in childhood. *Nat Clin Pract Endocrinol Metab* 2008; **4**: 320–321.
- Goldfarb B. Pediatric endocrinology debate prescribing drugs to teens with pre-diabetes. *DOC News* 2007; **4**: 15–16.
- Cole TJ, Bellizzi MC, Flegal M, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; **320**: 1240–1243.
- American diabetes association. Standards of medical care in diabetes – 2009. *Diabetes Care* 2009; **32**: S13–S61.
- Kay JP, Alemzadeh R, Langley G, D'Angelo L, Smith P, Holshouser S. Beneficial effects of metformin in normoglycemic morbidly obese adolescents. *Metabolism* 2001; **50**: 1457–1461.
- Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature: how to use an article about therapy and prevention. *JAMA* 1993; **270**: 2598–2601.
- Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinaemia and a family history of type 2 diabetes. *Paediatrics* 2001; **107**: e55(1–7).
- Srinivasan S, Ambler GR, Baur LA, Garnett SP, Tepsa M, Yap F, Ward GA, Cowell CT. Randomised controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. *J Clin Endocrinol Metab* 2006; **96**: 2074–2080.
- Love-Osborne K, Sheeder J, Zeitler P. Addition of metformin to a lifestyle modification program in adolescents with insulin resistance. *J Paediatr* 2008; **152**: 817–822.
- Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. *J Pediatr Endocrinol Metab* 2008; **21**: 339–348.
- Burgert TS, Duran EJ, Goldberg-Gell R, Dziura J, Yeckel CW, Katz S, Tamborlane WV, Caprio S. Short-term metabolic and cardiovascular effects of metformin. *Pediatr Diabetes* 2008; **9**: 567–576.
- Gordon-Larsen P, Nelson MC, Popkin BM. Longitudinal physical activity and sedentary behaviour trends: adolescence to adulthood. *Am J Prev Med* 2004; **27**: 277–283.
- Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. *Paediatr Res* 2006; **60**: 759–763.
- Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modelling. *Diabetes Care* 2004; **27**: 1487–1495.
- Monzillo LU, Hamdy O. Evaluation of insulin sensitivity in clinical practice and in research settings. *Nutr Rev* 2003; **61**: 397–412.

Appendix 1**Search strategy***Search for clinical insulin resistance*

1. exp insulin resistance
2. exp metabolic syndrome X
3. exp polycystic ovary syndrome
4. exp acanthosis nigricans
5. exp hyperinsulinaemia
6. exp insulin
7. exp glucose tolerance test
8. 1 or 2 or 3 or 4 or 5 or 6 or 7

Search for pre-diabetes

9. exp pre-diabetic state
10. exp glucose intolerance
11. 9 or 10

Search for specific population

12. exp child
13. exp adolescent
14. exp paediatrics
15. 9 or 10 or 11

Search for lifestyle interventions

16. exp lifestyle

Search for metformin interventions

17. exp metformin

Search for physical activity interventions

18. exp exercise or exercise therapy
19. exp physical education and training
20. resistance training.mp.
21. 18 or 19 or 20

Search for dietary interventions

22. exp diet and diet therapy
23. exp child nutrition physiology
24. exp adolescent nutrition physiology
25. exp dietary carbohydrates
26. exp dietary fats
27. 22 or 23 or 24 or 25 or 26
28. 8 or 11
29. 15 and 16 and 28
30. 15 and 17 and 28
31. 15 and 21 and 28
32. 15 and 27 and 28
33. 29 or 30 or 31 or 32
34. 33 limited to randomized control trials