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Abstract

Objective: Excess visceral adipose tissue (VAT) in children with obesity is associated with development of cardiovascular and metabolic disease. This meta-analysis investigated if lifestyle interventions can reduce VAT in overweight and obese youth.

Methods: Pubmed, Cochrane and PEDro were searched for clinical trials that objectively assessed VAT and included study arms with supervised diet, exercise or a combination. If there was a 'no-therapy' control group, the data of the control group and the intervention groups were used to meta-analyze the data. In all other cases the pre-intervention and the post-intervention data were used to meta-analyze. Effect sizes were calculated as standardized mean differences or changes of VAT and expressed as Hedges' g.

Results: The overall weighted mean effect size on VAT of all included interventions was -0.69 [95%CI = -0.90 to -0.48] ($p < 0.001$). Subgroup analysis showed that the overall weighted mean effect size of diet-only interventions on VAT was 0.23 [95%CI = -0.22 to 0.68] ($p = 0.311$). Interventions that combined diet and exercise showed a pooled effect size on VAT of -0.55 [95%CI = -0.75 to -0.39] ($p < 0.001$). The pooled effect size of exercise-only interventions on VAT was -0.85 [95%CI = -1.20 to -0.57] ($p < 0.001$).

Conclusions: Supervised exercise-only or combined diet and exercise interventions can reduce VAT in overweight and obese children and adolescents. The strongest effect was found in exercise-only groups. However, high quality RCT's describing the effect of supervised dietary interventions on VAT in children are lacking.

Key words: Intra-abdominal fat; Exercise therapy; Diet therapy; Pediatric obesity

Introduction

Prevalence of childhood obesity remains high both in the United States and in Europe and shows little decline.(34, 35, 59) Childhood obesity can be considered a probable early marker for adult obesity.(3) Modification of lifestyle (reduced caloric intake and increased physical activity) remains the cornerstone of a multidisciplinary approach in the treatment of childhood obesity.(22) All too often the focus remains on weight loss when defining success of lifestyle intervention programs for children with obesity.

Combining diet and exercise can yield important short-term reductions in metabolic risk such as improving HDL-C and insulin levels.(25) This can be important because childhood obesity seems to be associated with an increased risk for cardiovascular disease, type 2 diabetes and premature mortality as an adult, although more data is needed to elucidate the role of weight status as an adult.(27, 33, 39, 42) However, even at a young age, obesity is associated with increased metabolic risks. About one in every 10 adolescents between 12 and 19 years in the U.S. has metabolic syndrome. The prevalence of metabolic syndrome increases with BMI status, and ranges from 10% to 66% in obese adolescents.(17, 56) The burden of metabolic syndrome is associated with abdominal obesity in adolescents, which in turn is associated with insulin resistance.(23, 50) Intra-abdominal fat accumulation in adolescents is associated with an increased risk for cardiovascular disease and with both the metabolic and the inflammatory components of the metabolic syndrome.(49) This is why it is important to look beyond weight loss when treating childhood obesity.

Imaging techniques can be used to objectively assess visceral adipose tissue (VAT). MRI and CT are considered the gold standards to assess VAT, with an underestimation of VAT areas by MRI compared to CT.(29, 48) Although there seems to be an increased use of pediatric CT protocols to reduce radiation exposure to children, an apparent advantage of MRI is that it doesn't use radiation. The use of ultrasound is regarded as a good alternative method for the assessment of VAT.(43, 48) However, the reproducibility of ultrasound remains a concern.(48) Therefore well-trained examiners are needed.(43)

Targeting abdominal obesity, and visceral adipose tissue in particular, can be an important clinical goal in tackling obesity in children or adolescents. It has been demonstrated that both diet and exercise can reduce visceral adipose tissue in adults with overweight or obesity.(12, 44, 55) However, meta-analytical support for the systematic implementation of supervised exercise training and/or diet to reduce VAT in children/adolescents is currently unavailable. This is however, important to guide clinicians in their therapeutic options when dealing with children or adolescents with obesity.

Therefore, the aim of this systematic review and meta-analysis was to evaluate the effect of supervised lifestyle interventions (diet, exercise or a combination) on visceral adipose tissue in overweight and obese children and adolescents.

Review

This systematic review and meta-analysis was written according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was submitted to the PROSPERO register with registration number CRD42014015381.

Study selection and data extraction

Pubmed, Cochrane and PEDro were searched for controlled and uncontrolled clinical trials with a study arm that received supervised diet, exercise or a combination, and objectively assessed visceral adipose tissue by medical imaging (CT, MRI, Ultrasound), in children/adolescents with obesity, using algorithms based on adequate combinations of the following keywords: "intra-abdominal fat"; "visceral fat"; "exercise"; "diet, reducing"; "pediatric obesity"; "children"; "adolescent" with limits set to "children". Studies that did not fulfill these criteria were not eligible for inclusion. Studies published until September 2014 were eligible for inclusion. Corresponding authors were mailed when data were needed or information was missing. All studies were independently screened by two researchers on title, abstract and full text and duplicates were removed. Disagreements were resolved by discussion between the two review authors. If no consensus was reached, the opinion of a third researcher was asked.

Risk of bias

The Cochrane Collaboration's Tool for assessing risk of bias was used to assess the risk of bias of the included studies.(24) Two reviewers independently screened the included studies. Consensus was sought in case of disagreement.

Statistical analysis

If there was a 'no-therapy' control group, the data of the control group and the intervention groups were used to meta-analyze the data. In all other cases the pre-intervention and the post-intervention data were used to meta-analyze. A random-effects model was used for the overall meta-analysis while mixed-effects models were applied for subgroup analyses. Effect sizes were calculated as standardized mean differences or changes and expressed as Hedges' g to correct for possible small samples bias. Cochran's Q statistic and its corresponding p-value were calculated to test heterogeneity across the individual studies' effect sizes. Higgins' I^2 was computed and expressed as a percentage to assess the degree of this heterogeneity across the individual studies' effect sizes. To evaluate the effect of BMI changes on the effect size of changes in VAT, a meta-regression of the individual studies effect sizes of VAT-change over BMI-change was conducted. A subgroup analysis (a mixed model analysis) was conducted to assess the effect of the study design (a subgroup of studies without a 'no-therapy' control group and a subgroup of studies with a 'no-therapy' control group) on the overall weighted effect size. Statistical analyses were computed using the CMA-2 software (Comprehensive Meta-Analysis 2nd version, Biostat, Englewood, NJ, USA). Significance was set at 5%.

Results

The aim of this meta-analysis was to evaluate the effect of supervised diet or exercise (or a combination) intervention programs on visceral adipose tissue in children and adolescents with obesity. In the included studies change of VAT was objectively assessed using suitable medical imaging techniques with a high to very high accuracy for assessment of VAT.(48)

Results of the systematic literature search

The systematic literature search resulted initially in 120 articles, which were reduced to 13 articles (n = 792 participants; age range 7 to 19 years) after screening on title, abstract and full-text and after removal of duplicates.(2, 6, 9-11, 21, 31, 32, 37, 40, 46, 52, 53) (Fig 1) Characteristics of included studies are shown in table 1. Overall, the risk of bias of the included studies was perceived as fair, with poor scores for blinding and allocation concealment. A lack of a control group and small sample sizes increased the risk of bias in some studies. (Fig 2)

[Insert figures 1 and 2 somewhere here please]

Summary effect of lifestyle interventions

The overall weighted mean effect size of lifestyle interventions on VAT (expressed as Hedges' g) was -0.69 [95%CI = -0.90 to -0.48] with a Z-value of -6.37 (p <0.001). Between-studies heterogeneity was significant (Cochran's Q = 156.3; df(Q)=22; p ≤0.001) and high (I² =85.9%). A meta-regression showed that there was a greater decrease in VAT in studies with a greater decrease in BMI. The slope regression coefficient is 0.181 [95% CI = 0.136 to 0.226] and is highly significant (p<0.0001). (Fig 3)

[Insert figure 3 somewhere here please]

Subgroup analysis

Pre-specified subgroup analysis based on type of intervention (diet-only, diet + exercise or exercise-only) was conducted. (Fig 4)

The overall weighted mean effect size of the two diet-only intervention study-arms on VAT was 0.23 [95%CI = -0.22 to 0.68] with a Z-value of 1.01 (p =0.311). There was no statistically significant between-studies heterogeneity (Cochran's Q = 0.38; df(Q)=1; p =0.538; I² = 0.0%).

Interventions that combined diet and exercise showed an overall weighted mean effect size on VAT of -0.55 [95%CI = -0.75 to -0.39] with a Z-value of -5.37 (p <0.001) and a significant and high between-studies heterogeneity (Cochran's Q = 18.3; df(Q)=4; p =0.001; I² = 78.1%).

The overall weighted mean effect size of exercise-only interventions on VAT was -0.85 [95%CI = -1.20 to -0.57] with a Z-value of -5.40 ($p < 0.001$). Between-studies heterogeneity was significant and high (Cochran's $Q = 90.7$; $df(Q) = 15$; $p < 0.001$; $I^2 = 83.5\%$).

[Insert figure 4 somewhere here please]

Further subgroup analysis was conducted to evaluate the effect of the original study design on the observed weighted mean VAT effect size. The weighted mean effect sizes of the subgroup of studies without a 'no-therapy' control group and subgroup of studies with a 'no-therapy' control group were -0.762 and -0.491 respectively ($p = 0.132$). (Fig 5) Between studies heterogeneity was high in the first subgroup ($I^2 = 91.9\%$) but low in the latter group ($I^2 = 16.0\%$).

[Insert figure 5 somewhere here please]

Discussion

The results of this meta-analysis showed that combined exercise and diet interventions, or exercise-only interventions resulted in a significant decrease in VAT in overweight or obese children and adolescents. However, this effect was not seen in diet-only interventions. At first glance, these data seem to indicate that especially exercise interventions should be preferred to lower VAT in children and adolescents with obesity. However, the latter suggestion is raised with great caution. We could identify only one study with a diet-only intervention in children with obesity that assessed change in VAT.(40) In this study, change in hepatic lipid content was the primary outcome. The sample size of this study was relatively small with 16 children with obesity with fatty liver that completed the study, nine in the low-fat diet group and seven in the low glycemic load diet group. Although weight loss after six months was not significant and only modest (-1.5 ± 1.0 kg and -0.7 ± 1.1 kg in the low-fat and low glycemic load groups respectively), there was a significant decrease in BMI (kg/m^2 and z-score) and hepatic lipid (%) in both groups after six months. However, a non-significant increase in visceral fat (cm^3), measured by MRI, was reported in both groups. Interestingly, in adults, it has been reported that loss of visceral fat is greatest during the initial period of modest weight loss.(7) Moreover, greater weight loss ($> 20\%$) could cause preferential loss of subcutaneous adipose tissue over VAT. By meta-analyzing the effect of diet and/or exercise on VAT in overweight and obese

children and adolescents it has become evident that there is a clear need for well-designed, well-powered randomized controlled trial studies that include diet-only intervention groups.

Both in the combined exercise+diet and exercise-only subgroups there was a significant decrease of VAT. A meta-analysis of the effect of exercise on VAT in overweight adults also has demonstrated that exercise, even without a hypocaloric diet, has the potential to reduce VAT, after only 12 weeks.(55) Aerobic exercise training can reduce hepatic lipid content and visceral fat, independent of weight change in adults.(26) In children, change in weight or BMI should be interpreted with caution, keeping the normal weight gain over time in growing children in mind. However, most of the intervention groups, and indeed some of the control groups, showed a decrease in BMI. Sometimes, no information on BMI change in study groups was given. The study of Barbeau et al.(2) was the only study where both the intervention group and control group showed a slight increase in BMI, but the increase in VAT was far larger in the control group compared to the intervention group where VAT barely increased. In this study the intervention group received the opportunity to choose a healthy snack before they started with a mix of aerobic training and strength training with the focus on moderate to vigorous physical activity of 80 min, 5x/week, for 10 months. The study of Barbeau et al. did not limit the subjects to youths who were obese at baseline. Indeed, one aspect to the project rationale was to see if exercise alone could have a favorable influence on youths who vary across the whole spectrum of body fatness - i.e., prevent general and visceral obesity. Therefore, the results of that paper can be interpreted as being applicable to black girls who vary in body composition.

Although it was an after school physical activity program, the mean attendance to the intervention program was 54% in the study of Barbeau et al. Most of the included studies did not report the exercise adherence, which can be regarded as a limitation of this review. However, it has been suggested that the type, intensity, and duration of exercise of lifestyle intervention programs to promote weight loss in obese youth should be based on producing an acceptable adherence to exercise programs.(13, 18)

The duration of the interventions of the included studies ranged from three months to one year. Most included studies focused on aerobic exercise or a combination of aerobic and resistance training. Although resistance training will not result in weight loss in adults, there is some

evidence that it can yield loss of body fat and an increase of lean body mass.(15) The same goes for the use of resistance training in children with overweight or obesity.(14, 47) This is why weight loss exercise programs often offer a mix of aerobic and strengthening exercises. Both studies of Lee et al. were the only of the included studies that had a resistance training-only group.(31, 32) In both studies the protocol of the resistance training (and the aerobic training) were the same. In both studies changes after three months were reported, although VAT was expressed in kg in the 2012 study(31) and in cm^2 in the 2013 study(32). Intriguingly, in the study of 2012 the sample consisted of obese adolescent boys and the decrease of VAT in the resistance exercise group was higher than in the aerobic exercise group (-0.2 ± 0.04 kg and -0.1 ± 0.04 kg respectively), both significantly different compared to the control group where there was an increase of 0.2 ± 0.1 kg. However, in the study of 2013 the sample consisted of obese adolescent girls and this time the decrease of VAT was lower in the resistance exercise group than in the aerobic exercise group (-4.52 ± 7.23 cm^2 and -15.68 ± 7.64 cm^2 respectively), only the aerobic exercise group differed significantly from the control group, where there was an increase of 5.87 ± 7.16 cm^2 . It has been demonstrated in adults that reduction of VAT associated with weight loss, can be obesity phenotype- and gender-specific, with more reduction in VAT in men than women and in individuals with an intra-abdominal fat phenotype than individuals with an abdominal subcutaneous fat phenotype.(16, 36, 41)

A chronic low-grade inflammation that is associated with obesity, and excess visceral fat in particular, seems to play a crucial role in the development of endothelial dysfunction, secretion of inflammatory adipokines, cardiovascular disease, insulin resistance and the metabolic syndrome.(57) About 10% of adolescents in the U.S. has metabolic syndrome, which is an indication of an increased risk for type 2 diabetes and cardiovascular disease, and the prevalence is associated with BMI status (17, 56) and abdominal obesity in adolescents.(23, 50) Although exercise training does not consistently seems to improve blood lipid profile or decrease weight in children and adolescents with obesity, it is associated with beneficial changes in body composition and endothelial function.(58) Recently it was found that a supervised program consisting of diet and exercise can improve endothelial function in children with obesity, initiating a biphasic response: an increase in endothelial progenitor cells after five months and a decrease of endothelial microparticles after ten months.(4) When abdominal fat is accumulated

as visceral fat in favor of subcutaneous fat, a disturbance in adipokine secretion, a decrease of insulin sensitivity and a deteriorated metabolic profile is more likely to occur in obese youth.(5, 20, 51) Even at an early age (7 – 11 years), an association was found between VAT and cardiovascular risk factors such as increased blood lipid and lipoprotein concentrations, in boys and girls with obesity.(38) Moreover, excess VAT storage in adolescents with obesity increases the prevalence of non-alcoholic fatty liver disease.(8)

Therefore, normalizing the accumulation of VAT should be one of the therapeutic goals in treating obesity in children or adolescents. This meta-analysis provides evidence that exercise, alone or combined with diet, can help decrease VAT in overweight and obese children and adolescents. However, more studies are needed to find out if loss of VAT due to lifestyle interventions in youth can also be specific for gender or obesity phenotype. Future studies also need to determine what types of exercise, duration and intensity are most effective in reducing VAT in children or adolescents with obesity.

We acknowledge some limitations in this meta-analysis and systematic review that might provide opportunities for future research. We have limited our search to 3 databases. We have also focused on weight reducing dietary interventions by choosing “diet, reducing”, but not “dietary intervention” as a keyword. Although we used no limits or filters for period or language in the database search, we have applied “child” as a filter (birth – 18 years). Studies that have mixed groups of young adults and adolescents might be missed by the use of such a filter.

From a clinical perspective, there is a need for studies that look at the effect of diet and/or exercise programs on VAT in overweight or obese youth and concurrently study the effect on anthropometric variables such as waist circumference (WC) or sagittal abdominal diameter (SAD). Although there is some evidence that SAD is a better estimate of VAT volume than WC in women with obesity (19), more research is needed to recommend SAD for clinical use in children.(1, 30) Although WC is a measure that can be easily measured by clinicians, there is some conflicting evidence indicating that WC might not always be an accurate measure to assess changes in VAT in adults.(45, 54) Also in preschool children, anthropometric variables such as WC do not seem to provide a good assessment of VAT.(28) It remains a fact that two individuals

with a comparable WC, can have a different ratio between VAT and subcutaneous abdominal adipose tissue.

Conclusions

This meta-analysis provided evidence that supervised exercise-only or combined diet and exercise interventions have the potential to reduce VAT in overweight and obese children and adolescents, with the strongest effect found in the supervised exercise-only group. However, high quality RCT's describing the effect of supervised dietary interventions on VAT in such youth are lacking.

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Figures and captions

Figure 1. Four-phase flow diagram of the systematic reviewing process.

Figure 2. Risk of bias graph: consensus judgments about each risk of bias item presented as percentages across all 13 included studies.

Figure 3. Meta-analysis regression of the change in VAT according to the change in BMI.

Figure 4. Forest plot of the effects found on VAT in the individual studies, per subgroup, and the overall effect.

Figure 5. Forest plot of the effects found on VAT in studies that had a ‘no-therapy’ control group and studies in which the effect was not compared to a ‘no-therapy’ control group (pre- vs. post-intervention data analyses).

Figure 1

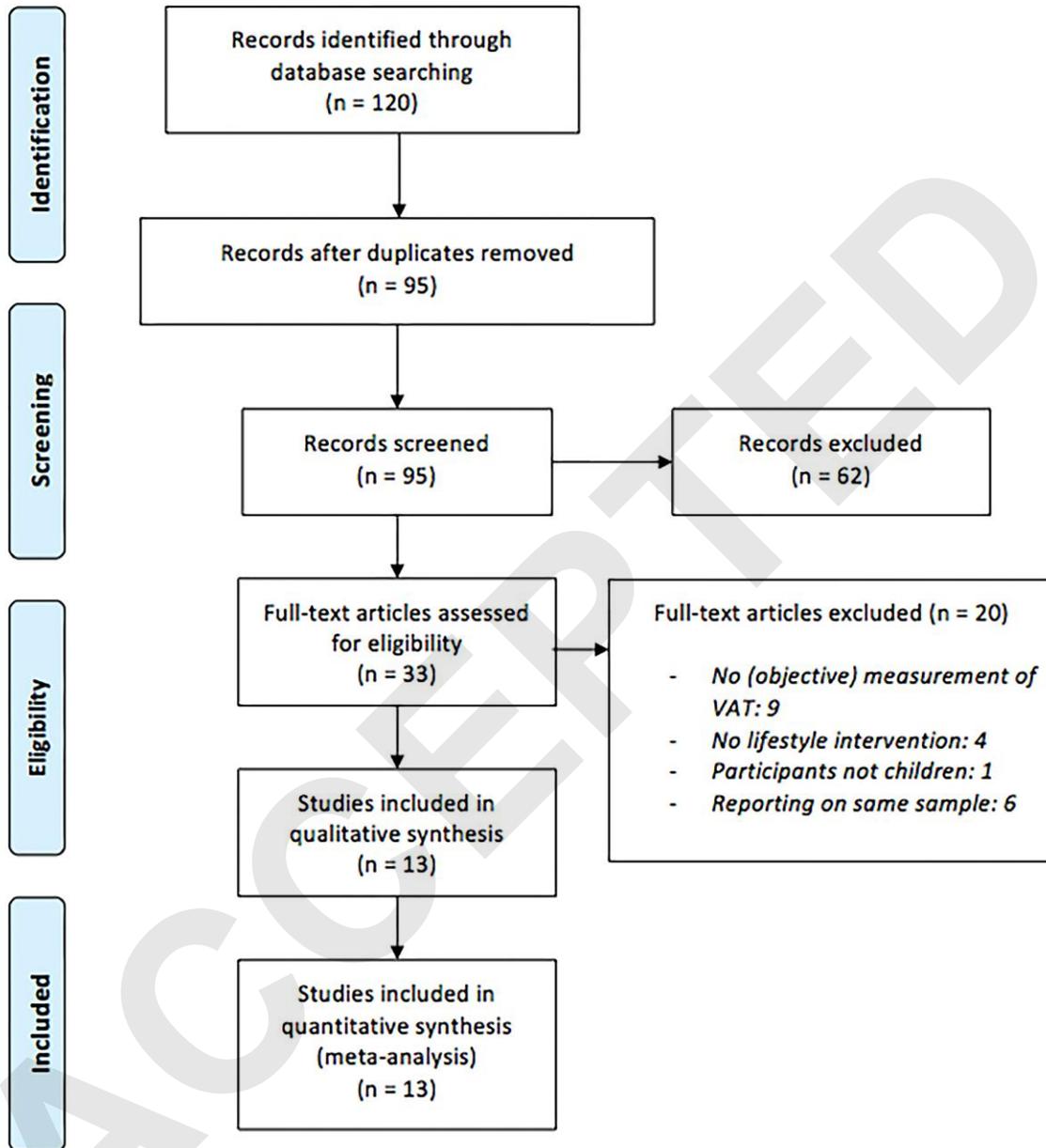


Figure 2

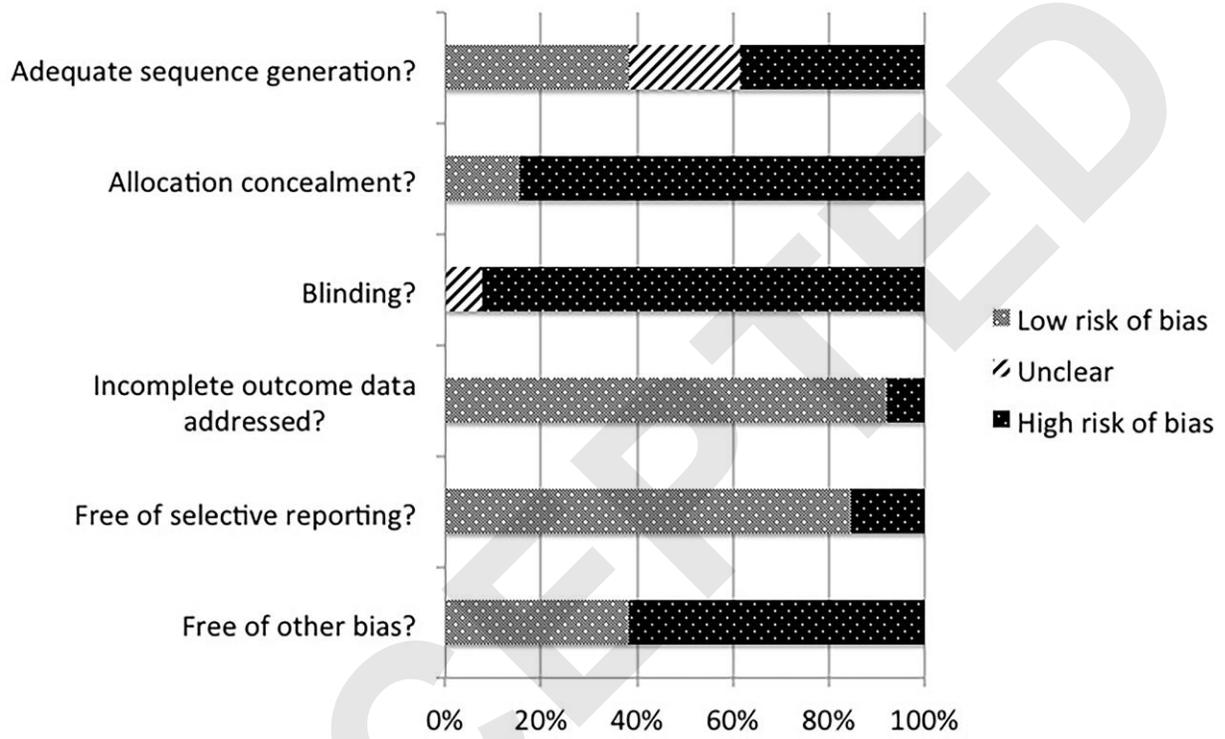


Figure 3

